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PHARMACOPEIAL FORUM VOL. 29 NO. 4 **JULY–AUG. 2003**

* The *USP–NF* (*USP26–NF21*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

Please address comments on *PF* content to Executive Secretariat
USP–NF, 12601 Twinbrook Pkwy.
Rockville, MD 20852

Telephone: 1-301-816-8345
Fax: 1-301-816-8373
http://www.usp.org

Pharmacopeial Forum is covered in *Current Contents/Life Sciences* and in the *Science Citation Index (SCI),* in *International Pharmaceutical Abstracts*, and in *Current Awareness in Biological Sciences.*

The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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Fax: (301) 816-8148.

STANDARDS DEVELOPMENT

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

USP publishes *Pharmacopeial Forum* (*PF*) bimonthly as the working vehicle of the USP Council of Experts. *PF* provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the *United States Pharmacopeia* and the *National Formulary* (*USP–NF*).

PF includes the following:

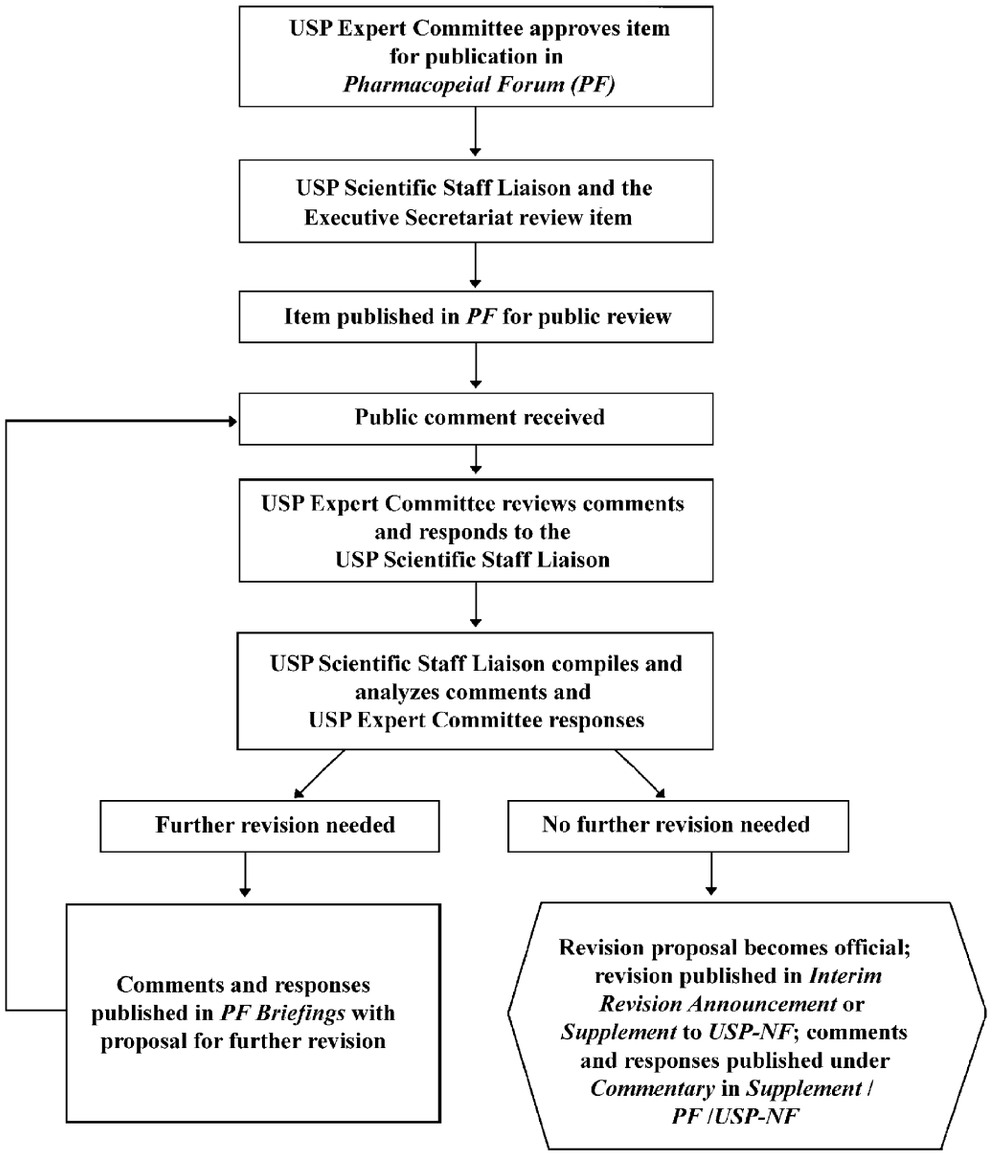
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official and binding before the publication of the next *USP–NF* or *Supplement* (*Interim Revision Announcement*)

USP welcomes comments and data on potential, proposed, or official standards.* Comments, along with USP's responses, will be published either in *PF Briefings*, the *Commentary* section of *PF*, the *Commentary* section of *Supplements* to *USP–NF*, or the *Commentary* section of *USP–NF*.

* If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before the section *Chromatographic Reagents Used in USP–NF and PF*.

The chart below shows the public review and comment process and its relationship to standards development.

Public Review and Comment Process for Standards Development



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

HOW TO USE *PF*

This section provides descriptions of the various parts of *PF*. It also includes *Committee Designations* and the *Staff Directory*.

The contents of the different sections of *PF* are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the *Staff Directory*) if they have any questions. A more detailed description of each section is provided at the beginning of that section.

Proposed and Adopted Revisions

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

Other Sections

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

Staff Directory
Names of all USP scientific staff liaisons with contact information.

Policies and Announcements
- General scientific and policy issues affecting *USP–NF* standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules

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

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

Index
Cumulative directory for the content of all issues of *PF* beginning with *PF* 29(1).

Reference Standards Catalog
List of official USP Reference Standards specified in *USP–NF*, along with availability and ordering information.

Chromatographic Reagents Used in USP–NF* and *Pharmacopeial Forum
Update of chromatographic reagents based on the proposals published in this issue of *PF*.

EXPERT COMMITTEE DESIGNATIONS*

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

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

* **HDQ** Indicates USP Headquarters items.
† The Expert Committee has been renamed. The old name, Excipients—Substances and Characterization (ESC) has been changed to Excipient Monograph Content (EMC).

STAFF DIRECTORY

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

STAFF	E-MAIL	PHONE	ASSIGNMENT
Clydewyn M. Anthony, Senior Scientific Associate	cma@usp.org	(301) 816-8139	Pharmaceutical Analysis 1 (PA1)
Frank P. Barletta, Consultant	fpb@usp.org	(301) 816-8328	Pharmaceutical Waters (PW)
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Lokesh Bhattacharyya, Senior Scientist	lb@usp.org	(301) 816-8201	Blood and Blood Products (BBP); Vaccines, Virology, and Immunology (VVI)
Barbara A. Bowman, Manager, Administrative Services	bab@usp.org	(301) 816-8278	USP Correspondence
William E. Brown, Scientist	web@usp.org	(301) 816-8380	Biopharmaceutics (BPC); Biostatistics (BST)
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Roger Dabbah, Director, Complex Actives	rd@usp.org	(301) 816-8336	
Behnam Davani, Scientist	bd@usp.org	(301) 816-8394	Pharmaceutical Analysis 7—Antimicrobial and Antivirals (PA7b)
Ian F. DeVeau, Senior Scientist	ifd@usp.org	(301) 816-8178	Cell Therapy, Gene Therapy and Tissue Engineering (CGT); Veterinary Products and Natural Products Monographs
Lawrence Evans, Senior Scientific Associate	le@usp.org	(301) 816-8389	Pharmaceutical Analysis 6 (PA6); Dietary Supplements—Non-Botanicals (DSN)
L. Valentin Feyns, Director, Reference Standards Evaluation	lvf@usp.org	(301) 816-8121	USP Reference Standards
John W. Gasper, Director, Executive Secretariat	jg@usp.org	(301) 816-8241	General Issues
Gabriel I. Giancaspro, Senior Scientist and Latin American Liaison	gig@usp.org	(301) 816-8343	Dietary Supplements—Botanicals (DSB); Dietary Supplements— Bioavailability and Nutrient Absorption (BNA)
Elena Gonikberg, Scientist	eg@usp.org	(301) 816-8251	Pharmaceutical Analysis 4 (PA4)

STAFF DIRECTORY *(continued)*

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Margareth R. Marques, Scientist and Latin American Liaison	mrm@usp.org	(301) 816-8106	Biopharmaceutics (BPC); Reagents
Alan W. Nichols, Director, Reference Standards Production	awn@usp.org	(301) 816-8321	USP Reference Standards
Claudia C. Okeke, Associate Director	cco@usp.org	(301) 816-8243	Compounding Pharmacy (CRX); Parenteral Products—Compounding and Preparation (PPC); Packaging, Storage, and Distribution (PSD)
W. Larry Paul, Scientific Fellow	wlp@usp.org	(301) 816-8331	Nomenclature and Labeling (NL); Pharmaceutical Dosage Forms (PDF)
Horacio Pappa, Scientist and Latin American Liaison	hp@usp.org	(301) 816-8319	Pharmaceutical Dosage Forms (PDF)
David A. Porter, Associate Director	dap@usp.org	(301) 816-8225	Analytical Microbiology (AMB); Biotechnology and Natural Therapeutics and Diagnostics (BNT); General Toxicity and Biocompatibility (GTB)
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Karen A. Russo, Scientist	kar@usp.org	(301) 816-8379	Pharmaceutical Analysis 1 (PA1); Excipient New Monograph Development
Jennifer Salguero, Scientist	jxs@usp.org	(301) 816-8371	Dietary Supplement Information
Salvador Salado, Scientist and Latin American Liaison	ss@usp.org	(301) 816-8165	Pharmaceutical Analysis 3 (PA3)
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Catherine M. Sheehan, Senior Scientific Associate	cxs@usp.org	(301) 816-8262	Excipient Monograph Content (EMC)
Eric B. Sheinin, Vice President, Information and Standards Development	es@usp.org	(301) 816-8103	
Andrzej Wilk, Senior Scientific Associate	aw@usp.org	(301) 816-8305	Pharmaceutical Analysis 5 (PA5); Radiopharmaceuticals and Medical Imaging (RMI)
William W. Wright, Scientific Fellow	www@usp.org	(301) 816-8335	Pharmaceutical Analysis 7—Antibiotics (PA7a)
Kahkashan Zaidi, Scientist	kxz@usp.org	(301) 816-8269	Aerosols (AER)

POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on *USP–NF* standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

USP CONFERENCE ON BIOLOGICAL AND BIOTECHNOLOGICAL DRUG SUBSTANCES AND PRODUCTS, NOVEMBER 18–23, 2003

This conference will be held in the Marriot Crystal City Gateway in Crystal City, Virginia. It is intended for those responsible for the development and maintenance of quality standards in this field. There are several objectives for this meeting:

- To involve industry and regulatory agencies in the development of quality standards for these products
- To promote the utility of standards for these products as necessary from regulatory and quality perspectives
- To involve stakeholders in the development of the future USP blueprint these areas
- To promote the utility of USP as a neutral body bridging industry and the regulatory agencies for the benefit of public health.

This conference will consist of formal presentations and workshops led by nationally and internationally recognized experts in different areas of interest to the biological and biotechnological industry. Conference topics will include the following:

- Equivalence of biological and biotechnological drug substances and products
- Biotechnology-derived products
- Blood-derived products
- Vaccines
- Cell and gene therapy, and tissue engineering
- Bioassay
- Ancillary products.

For program information, contact Lokesh Bhattacharyya at 301-816-8201 or lb@usp.org. For conference registration information, call 301-816-8226, or register online at www.usp.org/conferences.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE *USP–NF.* We are pleased to announce the availability of the *USP Guideline for Submitting Requests for Revision to the USP–NF*. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Non-Prescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

NEW *DIETARY SUPPLEMENTS* SECTION OF THE *USP.* As previously noted in earlier Announcements, beginning with *USP 27–NF 22*, all dietary supplement monographs will appear in the new *Dietary Supplements* section of the *USP*. Also, the section of *Pharmacopeial Forum* that was formerly entitled *Nutritional Supplements* is being changed to *Dietary Supplements*. Monographs that formerly appeared in the *Nutritional Supplements* will subsequently appear in the new *Dietary Supplements* section of the *USP* when they become official. Therefore, in addition to retaining the monographs that are in the current *Nutritional Supplements* section, the new section will include the following dietary supplement monographs that will be moved from the *NF*:

Chamomille
Choline Bitartrate
Choline Chloride
Chondroitin Sulfate Sodium
Chondroitin Sulfate Sodium Tablets
Chromium Picolinate
Cranberry Liquid Preparation
Echinacea angustifolia
Echinacea angustifolia, Powdered
Echinacea angustifolia, Powdered Extract
Echinacea pallida
Echinacea pallida, Powdered
Echinacea pallida, Powdered Extract
Echinacea purpurea Root
Echinacea purpurea Root, Powdered Extract
Echinacea purpurea, Powdered
Eleuthero
Eleuthero, Powdered
Eleuthero, Powdered Extract
Feverfew

Feverfew, Powdered
Garlic
Garlic Delayed-Release Tablets
Garlic Fluidextract
Garlic, Powdered
Garlic, Powdered Extract
Ginger
Ginger Tincture
Ginger, Powdered
Ginkgo
Ginseng, American
Ginseng, American, Powdered
Ginseng, American, Powdered Extract
Ginseng, Asian
Ginseng, Asian Tablets
Ginseng, Asian Powdered
Ginseng, Asian, Powdered Extract
Glucosamine and Chondroitin Sulfate Sodium Tablets
Glucosamine Hydrochloride
Glucosamine Sulfate Potassium Chloride
Glucosamine Sulfate Sodium Chloride
Glucosamine Tablets
Goldenseal
Goldenseal, Powdered
Goldenseal, Powdered Extract
Hawthorn Leaf with Flower
Hawthorn Leaf with Flower, Powdered
Horse Chestnut
Horse Chestnut, Powdered
Horse Chestnut, Powdered Extract
Licorice
Licorice, Powdered
Licorice, Powdered Extract
Lipoic Acid, Alpha
Lipoic Acid, Alpha Capsules
Lipoic Acid, Alpha Tablets
Milk Thistle
Milk Thistle Capsules
Milk Thistle Tablets
Milk Thistle, Powdered
Milk Thistle, Powdered Extract
Red Clover
Red Clover Tablets
Red Clover, Powdered
Red Clover, Powdered Extract
St. John's Wort
St. John's Wort, Powdered
St. John's Wort, Powdered Extract
Saw Palmetto
Saw Palmetto Capsules
Saw Palmetto Extract
Saw Palmetto, Powdered
Selenomethionine
Valerian
Valerian Tablets
Valerian, Powdered
Valerian, Powdered Extract

CORRESPONDENCE ADDRESS CORRECTION

In order to respond to the Stimuli article "Review of the Media Selection and Incubation Conditions for the Compendial Sterility and Microbial Limit Tests," published in *Pharmacopeial Forum*, Vol. 28(6) [Nov.–Dec. 2002], page 2034, correspondence should be addressed to David A. Porter, 12601 Twinbrook Parkway, Rockville, MD 20852; email: DAP@usp.org. David A. Porter is Staff Liaison to the Expert Committee on Analytical Microbiology. Correspondence should not be sent to Anthony M. Cundell, Ph.D. at Wyeth-Ayerst Pharmaceuticals, as we originally published.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Barbara B. Hubert, Director, Pharmacopeial Education, BBH@usp.org, 301-816-8333, or Diana Lenahan, Program Associate, DPL@usp.org, 301-816-8530. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2003

Date	Name of course	Location
July 14 and 15	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
July 23	Analytical Method Validation	USP Headquarters, Rockville, MD
August 11 and 12	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
August 20	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
August 21	Standards 101: Advanced Use of *USP–NF*, General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
September 15 and 16	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
September 18	Fundamentals of Microbiological Testing	USP Headquarters, Rockville, MD
September 24	Fundamentals of Titration	USP Headquarters, Rockville, MD
October 8	Analytical Method Validation	USP Headquarters, Rockville, MD
October 20 and 21	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
November 17 and 18	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
December 8	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 9	Standards 101: Advanced Use of *USP–NF*, General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
December 15 and 16	Fundamentals of Dissolution	USP Headquarters, Rockville, MD

VISIT THE USP WEB SITE AT ⟨http://www.usp.org⟩. Various resources related to Pharmacopeial standards are presented, including highlights from *PF*.

***USP–NF* AVAILABLE IN THREE ELECTRONIC FORMATS**. The trusted reference for official pharmaceutical standards is available in three convenient electronic formats—CD, intranet, and online. The CD is ideal for single users who prefer to have *USP–NF* on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official *USP–NF* content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

***CHROMATOGRAPHIC REAGENTS* NOW AVAILABLE**. *Chromatographic Reagents* lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that have been published in *Pharmacopeial Forum* (*PF*) since 1980. *Chromatographic Reagents* also helps to track which column reagents were used to validate methods that have become official and are included in *USP–NF*. The branded column reagents list is updated bimonthly through *Pharmacopeial Forum*. *Chromatographic Reagents* can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the
European Pharmacopoeia Commission
B.P. 907
F 67029 Strasbourg Cedex 1
France

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
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E-mail: nakashima-nobumasa@mhlw.go.jp

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

Please note that *USP–NF* is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

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

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

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

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

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

PUBLICATION SCHEDULES

Publication	Publication Date	Official Date
1st Supplement	Feb. 2003	Apr. 1, 2003
PF 29(2) [Mar.–Apr. 2003]	Mar. 2003	Not Applicable
2nd IRA [published in *PF* 29(2)]	Mar. 2003	Apr. 1, 2003
PF 29(3) [May–June 2003]	May 2003	Not Applicable
3rd IRA [published in *PF* 29(3)]	May 2003	June 1, 2003
2nd Supplement	June 2003*	Aug. 1, 2003*
PF 29(4) [July–Aug. 2003]	July 2003*	Not Applicable
4th IRA [published in *PF* 29(4)]	July 2003*	Aug. 1, 2003*
PF 29(5) [Sept.–Oct. 2003]	Sept. 2003*	Not Applicable
5th IRA [published in *PF* 29(5)]	Sept. 2003*	Oct. 1, 2003*
PF 29(6) [Nov.–Dec. 2003]	Nov. 2003*	Not Applicable
6th IRA [published in *PF* 29(6)]	Nov. 2003*	Dec. 1, 2003*

* Tentative

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

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

Readers should review this section to determine if they are affected by any of the changes.

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ▪new text▪, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ▪▪, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement*, and ▪2S (*USP 26*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 26*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 26–NF 21*. The page number indicates where the item is found in *USP 26–NF 21*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in the next available annual edition or *Supplement*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

FOURTH INTERIM REVISION ANNOUNCEMENT to *USP 26* and to *NF 21*

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

Larry L. Braden, *Chair*
USP Board of Trustees

Roger L. Williams, *Executive Vice President* and *Chairman, USP Council of Experts*

John W. Gasper, *Director*, *Executive Secretariat*

Official August 1, 2003. **Released July 1, 2003.**

All inquiries and comments regarding *USP 26* text and *NF 21* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were indicated in past *Supplements to USP–NF* as being not yet available, have since become available. Thus, the official date of each *USP 26* or *NF 21* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Acesulfame Potassium RS (January 1, 2004)
USP Alendronate Sodium RS (November 1, 2003)
USP Aminopentamide Sulfate RS (September 1, 2003)
USP Amitraz RS (November 1, 2003)
USP Powdered Asian Ginsing Extract RS (September 1, 2003)
USP Betahistine Hydrochloride RS (January 1, 2004)
USP Brinzolamide RS (November 1, 2003)
USP Brinzolamide Related Compound A RS (November 1, 2003)
USP Brinzolamide Related Compound B RS (November 1, 2003)
USP Cefipime Hydrochloride RS (January 1, 2004)
USP Cefipime Hydrochloride System Suitability RS (January 1, 2004)
USP Cetyl Palmitate RS (November 1, 2003)
USP Choline Bitartrate RS (January 1, 2004)
USP Chondroitin Sulfate Sodium RS (September 1, 2003)
USP Clozapine RS (November 1, 2003)
USP Desogestrel RS (September 1, 2003)
USP Desogestrel Related Compound A RS (September 1, 2003)
USP Desogestrel Related Compound B RS (September 1, 2003)
USP Desogestrel Related Compound C RS (September 1, 2003)
USP Dextran V_o Marker RS (September 1, 2003)
USP Dextran 4 Calibration RS (November 1, 2003)
USP Dextran 10 Calibration RS (November 1, 2003)
USP Dextran 40 Calibration RS (November 1, 2003)
USP Dextran 70 Calibration RS (November 1, 2003)
USP Dextran 250 Calibration RS (November 1, 2003)
USP Diloxanide Furoate RS (November 1, 2003)
USP Dinoprostone RS (November 1, 2003)
USP Dorzolamide RS (November 1, 2003)
USP Dorzolamide Hydrochloride Related Compound A RS (January 1, 2004)
USP Emedastine Difumarate RS (November 1, 2003)
USP Ethinyl Estradiol Related Compound A RS (November 1, 2003)
USP Fenoldopam Related Compound A RS (January 1, 2004)
USP Fenoldopam Related Compound B RS (January 1, 2004)
USP Gemfibrozil Related Compound A RS (January 1, 2004)
USP Glutamic Acid RS (November 1, 2003)
USP Glutamine RS (September 1, 2003)
USP Glycyrrhizic Acid RS (November 1, 2003)
USP Hydroxypropyl Betadex RS (September 1, 2003)
USP Iodixanol RS (September 1, 2003)
USP Isoflupredone Acetate RS (January 1, 2004)
USP Ketamine Related Compound A RS (January 1, 2004)
USP Lansoprazole RS (November 1, 2003)
USP Lansoprazole Related Compound A RS (November 1, 2003)
USP Lynestrenol RS (September 1, 2003)
USP Powdered Milk Thistle Extract RS (November 1, 2003)
USP Milrinone RS (November 1, 2003)
USP Milrinone Related Compound A RS (November 1, 2003)
USP Monensin Sodium RS (September 1, 2003)
USP Nabumetone RS (January 1, 2004)
USP Norgestimate RS (January 1, 2004)
USP Oxaprozin RS (January 1, 2004)
USP Paroxetine Hydrochloride RS (September 1, 2003)
USP Poloxalene RS (November 1, 2003)
USP Quinapril Related Compound A RS (January 1, 2004)
USP Quinapril Related Compound B RS (January 1, 2004)
USP Ramipril RS (January 1, 2004)
USP Ramipril Related Compound A RS (January 1, 2004)
USP Repaglinide RS (September 1, 2003)
USP Repaglinide Related Compound A RS (September 1, 2003)
USP Repaglinide Related Compound B RS (September 1, 2003)
USP Repaglinide Related Compound C RS (September 1, 2003)
USP Sodium Starch Glycolate RS (January 1, 2004)
USP Tacrine Hydrochloride RS (January 1, 2004)
USP Taurine RS (January 1, 2004)
USP Tiletamine Hydrochloride RS (November 1, 2003)
USP Tinidazole RS (January 1, 2004)
USP Tinidazole Related Compound A RS (January 1, 2004)
USP Thalidomide RS (January 1, 2004)
USP Tylosin RS (November 1, 2003)
USP Urea C13 RS (January 1, 2004)
USP Zileuton RS (January 1, 2004)
USP Zileuton Related Compound A RS (November 1, 2003)
USP Zileuton Related Compound B RS (November 1, 2003)
USP Zileuton Related Compound C RS (November 1, 2003)

The official dates of any *USP 26* or *NF 21* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

USP Alteplase RS
USP Amiloxate RS
USP Positive Bioreaction RS
USP Cefpiramide RS
USP Cinoxate RS
USP Decoquinate RS
USP Desflurane RS
USP Desflurane Related Compound A RS
USP Dextran 40 RS
USP Dextran 70 RS
USP Diethylstilbestrol Diphosphate RS
USP Enalapril Related Compound B RS
USP Enzacamene RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS
USP Lactase RS
USP Medroxyprogesterone Acetate Related Compound A RS
USP Menotropins RS
USP Methyldopa–Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Hydrochloride RS
USP Ondansetron Related Compound A RS
USP Ondansetron Related Compound B RS
USP Ondansetron Related Compound C RS
USP Ondansetron Related Compound D RS
USP Oxfendazole RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Δ^8-tetrahydrocannabinol RS
USP Δ^9-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

NOTICE OF POSTPONEMENT

The following revision to the Prednisolone monograph, published in the *First Supplement* to *USP 26-NF 21* and originally scheduled to become official on April 1, 2003, has been postponed indefinitely. The revision was to have added a *Chromatographic purity* test and have deleted the *Ordinary impurities* test for Prednisolone. This postponement is to accommodate approved products on the market that cannot meet the requirement and is intended to provide sufficient time to evaluate a different proposal via the regular revision process.

The Expert Committee is reviewing a new proposal to reflect the approved products. The USP intends to publish this revised acceptance criteria in a future number of *Pharmacopeial Forum* for public review and comment.

Prednisolone

Add the following:

•**Chromatographic purity**—

Solution A—Prepare a filtered and degassed mixture of chloroform, methanol, and water (967.9:30:2.1).

Solution B—Prepare a filtered and degassed mixture of chloroform, methanol, and water (947.9:50:2.1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Test solution—Dissolve a suitable quantity of Prednisolone in *Solution A*, with the aid of sonication and shaking, to obtain a solution having a concentration of about 2.5 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L3. The flow rate is about 2.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–20	100	0	equilibration
20–30	100→0	0→100	linear gradient
30–50	0	100	isocratic
50–51	0→100	100→0	linear gradient
51–100	100	0	isocratic

Chromatograph the *Test solution*, and record the peak areas as directed for *Procedure:* the resolution, *R*, between prednisolone and any impurity is not less than 1.5; and the column efficiency is not less than 6000 theoretical plates.

Procedure—Inject a volume (about 5 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak areas. Calculate the percentage of each impurity in the portion of Prednisolone taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity; and r_s is the sum of the areas of all the peaks: not more than 0.6% of any individual impurity is found, and not more than 2.0% of total impurities is found.•4

•(Postponed Indefinitely)•4

Delete the following:

•**Ordinary impurities** ⟨466⟩—

Solvent: a mixture of alcohol and water (1:1).

Eluant: a mixture of toluene and isopropyl alcohol (70:30), in a nonequilibrated chamber.

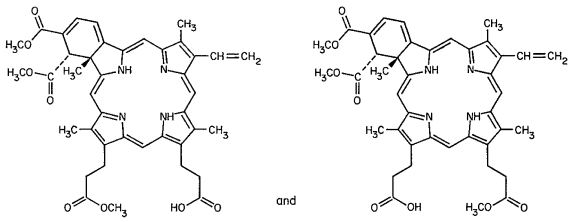
Visualization: technique 1.•4

•(Postponed Indefinitely)•4

USP 26 MONOGRAPHS

Add the following:

•Verteporfin



$C_{41}H_{42}N_4O_8$ 718.79

23*H*,25*H*-Benzo[*b*]porphine-9,13-dipropanoic acid, 18-ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-, monomethyl ester, *trans*.

(±)-*trans*-3,4-Dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropanoic acid, 3,4,9-trimethyl ester mixture with (±)-*trans*-3,4-dicarboxy-4,4a-dihydro-4a,8,14,19-tetramethyl-18-vinyl-23*H*,25*H*-benzo[*b*]porphine-9,13-dipropionic acid, 3,4,13-trimethyl ester [*129497-78-5*].

» Verteporfin contains not less than 94.0 percent and not more than 102.0 percent of $C_{41}H_{42}N_4O_8$, calculated on the anhydrous basis.

Caution—Verteporfin is a light-activated drug used in photodynamic therapy. Care should be taken to avoid contact with eyes and skin.

Packaging and storage—Preserve in tight containers, and store in a freezer.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Verteporfin RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩.

B: The retention times of the two major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 100 cfu per g.

Bacterial endotoxins ⟨85⟩: not more than 0.5 USP Endotoxin Unit per mg of verteporfin.

Water, *Method Ic* ⟨921⟩: not more than 1.4%.

Residue on ignition ⟨281⟩: not more than 0.2%.

Heavy metals, *Method I* ⟨231⟩: not more than 0.002%.

Related compounds—

Solution A, *Solution B*, and *Mobile phase*—Proceed as directed in the *Assay.*

Test solution—Prepare as directed for *Assay preparation* in the *Assay.*

Chromatographic system—Proceed as directed in the *Assay.* To evaluate the system suitability requirements, use the *Standard preparation* prepared as directed in the *Assay.*

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each related compound in the portion of Verteporfin taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the individual peak response of each related compound; and r_s is the sum of the responses of all of the peaks. Not more than 0.6% of the peak having a retention time of about 0.56 relative to that of the first verteporfin isomer peak is found, not more than 0.8% of any other individual related compound is found, and the sum of all impurities is not more than 4.0%.

Limit of methylene chloride—Use the procedure for *Method 1* under *Organic Volatile Impurities* ⟨467⟩, with the following exceptions:

Standard solution: 50 µg of methylene chloride per mL in dimethylformamide.

Test solution: 10 mg of Verteporfin per mL in dimethylformamide.

Limit: not more than 5,000 µg per g of Verteporfin (0.5%).

Assay—

Solution A—Prepare a filtered and degassed mixture of 1% (w/v) aqueous ammonium sulfate, acetonitrile, glacial acetic acid, and 3.6 M sulfuric acid (10:10:1:0.027).

Solution B—Prepare a filtered and degassed mixture of 1% (w/v) aqueous ammonium sulfate, tetrahydrofuran, glacial acetic acid, and 3.6 M sulfuric acid (10:10:1:0.034).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—To a suitable volumetric flask, transfer an accurately weighed quantity of USP Verteporfin RS sufficient to make a 0.25 mg per mL solution. Add a volume of a mixture of acetonitrile and tetrahydrofuran (1:1) equivalent to 60% of the flask volume, and dissolve. Dilute with water to volume, and mix. [NOTE—Protect the solution from light.]

Assay preparation—Transfer about 25 mg of Verteporfin, accurately weighed, to a 100-mL volumetric flask. Add 60 mL of a mixture of acetonitrile and tetrahydrofuran (1:1), and dissolve. Dilute with water to volume, and mix. [NOTE—Protect the solution from light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 410-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is 1.5 mL per minute. The column temperature is maintained at 30°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–60	80	20	isocratic
60–90	80→60	20→40	linear gradient
90–91	60	40	isocratic
91–120	60→30	40→70	linear gradient
120–121	30	70	isocratic
121–125	30→0	70→100	linear gradient
125–137	0	100	isocratic
137–140	0→80	100→20	linear gradient
140–150	80	20	isocratic

Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between the two verteporfin peaks is not less than 2.5; the tailing factor is not more than 1.3; and the relative standard deviation for replicate injections is not more than 2.0%.

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Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the verteporfin peaks. Calculate the quantity, in mg, of $C_{41}H_{42}N_4O_8$ in the portion of Verteporfin taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Verteporfin RS in the *Standard preparation;* and r_U and r_S are the sums of the peak responses of the two verteporfin regioisomer peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

Calculate the ratio of the peak responses for the two peaks assigned to verteporfin: not less than 0.9 and not more than 1.1.●4

NF 21 MONOGRAPHS

Red Clover

Change to read:

Content of isoflavones—

Solvent: a mixture of alcohol and water (1:1).

Solution A—Prepare a filtered and degassed mixture of water and acetonitrile (75:25) containing 0.05% trifluoroacetic acid.

Solution B—Use filtered and degassed acetonitrile containing 0.05% trifluoroacetic acid.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution 1—Dissolve an accurately weighed quantity of USP Powdered Red Clover Extract RS in 2 N hydrochloric acid (0.5 mL per each mg of Extract) with shaking for 1 minute and heating in a water bath for 30 minutes. Dilute with *Solvent* to obtain a solution having a known concentration of about 0.5 mg per mL. Filter through a membrane having a 0.45-µm or finer porosity.

Standard solution 2—Dissolve an accurately weighed quantity of USP Formononetin RS in a mixture of n-propanol and water (1:1) with sonication. Dilute quantitatively, and stepwise if necessary, with the mixture of n-propanol and water (1:1) to obtain a solution having a known concentration of about 0.1 mg per mL. Filter through a membrane having a 0.45-µm or finer porosity.

Test solution—Accurately weigh approximately 2500 mg of ground plant material, and place in a 120-mL flask with a stopper. Add exactly 100 mL of *Solvent*, close the flask, and shake on an orbital or wrist-action shaker for not less than 12 hours. Transfer 50.0 mL of this solution to a round-bottom flask, and evaporate to dryness under vacuum. Add 15 mL of 2 N hydrochloric acid, and heat in a water bath for 30 minutes. Quantitatively transfer this solution with the aid of about 15 mL of alcohol, to a 50-mL volumetric flask, and dilute with *Solvent* to volume. Filter through a membrane having a 0.45-µm or finer porosity, discarding the first 4 mL of filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains end-packed 5-µm packing L1. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 45°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–2	100	0	isocratic
2–2.5	100→87	0→13	linear gradient
2.5–7.5	87→80	13→20	linear gradient
7.5–7.8	80→73	20→27	linear gradient
7.8–8.0	73→55	27→45	linear gradient
8.0–11.0	55→50	45→50	linear gradient
11.0–13.0	50→40	50→60	linear gradient
13.0–15.0	40→26	60→74	linear gradient
15.0–16.0	26→0	74→100	linear gradient
16.0–18.1	0→100	100→0	linear gradient
18.1–23.0	100	0	isocratic

Chromatograph *Standard solution 1*, and record the peak responses as directed for *Procedure:* the chromatograms obtained are similar to the Reference Chromatogram provided with the USP Powdered Red Clover Extract RS; the tailing factor for formononetin is not more than 2.0; and the relative standard deviation for replicate injections of *Standard solution 1* is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of *Standard solution 1*, *Standard solution 2*, and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention times of the peaks corresponding to daidzein, genistein, formononetin, and biochanin A by comparison of the chromatogram of *Standard solution 1* with that obtained from the Reference Chromatogram. Separately calculate the percentages of daidzein, genistein, formononetin, and biochanin A in the portion of Red Clover taken by the formula:

$$50F(C/W)(r_U / r_S),$$

in which F is the conversion factor for each analyte (0.97 for daidzein, 1.13 for genistein, 1.00 for formononetin, and 1.05 for bioachanin A); C is the concentration, in mg per mL, of USP Formononetin RS in *Standard solution 2; W* is the weight, in g, of Red Clover taken to prepare the *Test solution;* ●r_U is the peak response for each relevant isoflavon obtained from the *Test solution;* and r_S is the peak response for formononetin obtained from *Standard solution 2*.●4

GENERAL CHAPTERS

General Tests and Assays

⟨11⟩ USP REFERENCE STANDARDS

Change to read:
USP Aminobenzoic Acid RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP Azatadine Maleate RS—•Do not dry. Keep container tightly closed.•4

Change to read:
USP Cefprozil (*Z*)-Isomer RS—•Do not dry. Keep container tightly closed. Store in a freezer.•4

Change to read:
USP Ceftriaxone Sodium RS—•Do not dry before using. Store in a refrigerator. After opening, store in a tightly closed container.•4

Change to read:
USP Choline Bitartrate RS—•Dry at 65° in vacuum for 4 hours before using. Keep container tightly closed. Store in a dessicator. This material is hygroscopic.•4

Change to read:
USP Cimetidine RS—•Do not dry. Keep container tightly closed. Protect from light. Store at room temperature.•4

Change to read:
USP Desflurane Related Compound A RS [bis-(1,2,2,2-tetrafluoroethyl)ether] ($C_4H_2F_8O$ ✧ 218.05)•—Do not dry. After opening the ampul, store in a tightly closed container. Store in a refrigerator.•4

Change to read:
USP Desoxycorticosterone Acetate RS—•Do not dry. Keep container tightly closed.•4

Change to read:
USP Dichlorphenamide RS—•Do not dry. Keep container tightly closed.•4

Change to read:
USP Emedastine Fumarate RS—•Dry portion at 105° for 3 hours before using. Keep container tightly closed.•4

Change to read:
USP Ethinyl Estradiol RS—•Dry portion at 105° for 3 hours before using. Keep container tightly closed. Protect from light.•4

Change to read:
USP Gemfibrozil Related Compound A RS [2,2-dimethyl-5-[2,5-dimethyl-4-propene-1-yl)phenoxy]valeric acid] ($C_{18}H_{26}O_3$ ✧ 290.40)—•Do not dry. Keep container tightly closed. Store at room temperature. [*Caution—Solutions are light-sensitive.*]•4

Change to read:
USP Glycopyrrolate RS—•Do not dry. Keep container tightly closed.•4

Change to read:
USP Levamisole Hydrochloride RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP L-Lysine Acetate RS—•Do not dry. Keep container tightly closed.•4

Change to read:
USP Mefenamic Acid RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP Nifedipine RS—•Do not dry. Keep container tightly closed. Avoid exposure to light. Handle with care.•4

Change to read:
USP Poloxalene RS—•Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.•4

Change to read:
USP Progesterone RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP Sodium Ascorbate RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP Tacrine Hydrochloride RS—•Do not dry. Determine the water content titrimetrically at the time of use. Keep container tightly closed. Store at room temperature. Protect from light.•4

Change to read:
USP Thiothixene RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP Tinidazole RS—•Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.•4

Change to read:
USP Tinidazole Related Compound A RS [(2-methyl-5-nitroimidazole] ($C_4H_5N_3O_2$ ✧ 127.10)—•Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.•4

Change to read:
USP Tobramycin RS—•Do not dry before using. Store in a freezer, protect from light, and allow to attain room temperature before opening. After opening the ampul, store the material in a tightly closed container.•4

Change to read:
USP Trimethoprim RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP Ubidecarenone RS—•Do not dry. Keep container tightly closed. Protect from light.•4

Change to read:
USP Zileuton RS—•Do not dry. Keep container tightly closed. Store at room temperature under nitrogen. Protect from light.•4

Interim Revision Announcement

Change to read:

USP Zileuton Related Compound A RS [*N*-(1-Benzo-[*b*]thien-2-ylethyl)urea**]** ($C_{11}H_{12}N_2OS$ ✧ •220.30)—Do not dry. Keep container tightly closed. Store at room temperature under nitrogen. Protect from light.•4

Change to read:

USP Zileuton Related Compound B RS [2-(Benzo[*b*]thien-2-oyl)benzo[*b*]thiopene**]** ($C_{17}H_{10}OS_2$ ✧ •294.40)—Do not dry. Keep container tightly closed. Store at room temperature under nitrogen. Protect from light.•4

Change to read:

USP Zileuton Related Compound C RS [1-Benzo-[*b*]thien-2-ylethanone**]** ($C_{10}H_8OS$ ✧ •176.24)—Do not dry. Keep container tightly closed. Store at room temperature under nitrogen. Protect from light.•4

Change to read:

⟨71⟩ STERILITY TESTS

•◆Portions of this general chapter have been harmonized with the corresponding texts of the European Pharmacopeia and/or the Japanese Pharmacopeia. Those portions that are not harmonized are marked with symbols (◆ ◆) to specify this fact.◆

The following procedures are applicable for determining whether a Pharmacopeial article purporting to be sterile complies with the requirements set forth in the individual monograph with respect to the test for sterility. Pharmacopeial articles are to be tested by the *Membrane Filtration* method under *Test for Sterility of the Product to be Examined* where the nature of the product permits. If the membrane filtration technique is unsuitable, use the *Direct Inoculation of the Culture Medium* method under *Test for Sterility of the Product to be Examined*. All devices, with the exception of *Devices with Pathways Labeled Sterile*, are tested using the *Direct Inoculation of the Culture Medium* method. Provisions for retesting are included under *Observation and Interpretation of Results*.

Because sterility testing is a very exacting procedure, where asepsis of the procedure must be ensured for a correct interpretation of results, it is important that personnel be properly trained and qualified. The test for sterility is carried out under aseptic conditions. In order to achieve such conditions, the test environment has to be adapted to the way in which the sterility test is performed. The precautions taken to avoid contamination are such that they do not affect any microorganisms that are to be revealed in the test. The working conditions in which the tests are performed are monitored regularly by appropriate sampling of the working area and by carrying out appropriate controls.

These Pharmacopeial procedures are not by themselves designed to ensure that a batch of product is sterile or has been sterilized. This is accomplished primarily by validation of the sterilization process or of the aseptic processing procedures.

When evidence of microbial contamination in the article is obtained by the appropriate Pharmacopeial method, the result so obtained is conclusive evidence of failure of the article to meet the requirements of the test for sterility, even if a different result is obtained by an alternative procedure. For additional information on sterility testing, see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩.•4

MEDIA

Prepare media for the tests as described below, or dehydrated formulations may be used provided that, when reconstituted as directed by the manufacturer or distributor, they meet the requirements of the *Growth Promotion Test of Aerobes, Anaerobes, and Fungi*. Media are sterilized using a validated process.

The following culture media have been found to be suitable for the test for sterility. *Fluid Thioglycollate Medium* is primarily intended for the culture of anaerobic bacteria. However, it will also detect aerobic bacteria. *Soybean–Casein Digest Medium* is suitable for the culture of both fungi and aerobic bacteria.

Fluid Thioglycollate Medium

L-Cystine	0.5 g
Sodium Chloride	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	5.5/5.0 g
Agar, granulated (moisture content not exceeding 15%)	0.75 g
Yeast Extract (water-soluble)	5.0 g
Pancreatic Digest of Casein	15.0 g
Sodium Thioglycollate	0.5 g
or Thioglycolic Acid	0.3 mL
Resazurin Sodium Solution (1 in 1000), freshly prepared	1.0 mL
Purified Water	1000 mL

Mix the L-cystine, sodium chloride, dextrose, yeast extract, and pancreatic digest of casein with the purified water, and heat until solution is effected. Dissolve the sodium thioglycollate or thioglycolic acid in the solution and, if necessary, add 1 N sodium hydroxide so that, after sterilization, the solution will have a pH of 7.1 ± 0.2. If filtration is necessary, heat the solution again without boiling, and filter while hot through moistened filter paper. Add the resazurin sodium solution, mix, and place the medium in suitable vessels that provide a ratio of surface to depth of medium such that not more than the upper half of the medium has undergone a color change indicative of oxygen uptake at the end of the incubation period. Sterilize using a validated process. If the medium is stored, store at a temperature between 2° and 25° in a sterile, airtight container. If more than the upper one-third of the medium has acquired a pink color, the medium may be restored once by heating the containers in a water-bath or in free-flowing steam until the pink color disappears and by cooling quickly, taking care to prevent the introduction of nonsterile air into the container.

Fluid Thioglycollate Medium is to be incubated at 32.5 ± 2.5°.

◆Alternative Thioglycollate Medium

Prepare a mixture having the same composition as that of the *Fluid Thioglycollate Medium*, but omitting the agar and the resazurin sodium solution, sterilize as directed above, and allow to cool prior to use. The pH after sterilization is 7.1 ± 0.2. Incubate under anaerobic conditions for the duration of the incubation period.

Alternative Fluid Thioglycollate Medium is to be incubated at 32.5 ± 2.5°.◆

Soybean–Casein Digest Medium

Pancreatic Digest of Casein	17.0 g
Papaic Digest of Soybean Meal	3.0 g
Sodium Chloride	5.0 g
Dibasic Potassium Phosphate	2.5 g
Dextrose ($C_6H_{12}O_6 \cdot H_2O$)	2.5/2.3 g
Purified Water	1000 mL

Dissolve the solids in the purified water, heating slightly to effect a solution. Cool the solution to room temperature, and adjust the pH with 1 N sodium hydroxide so that, after sterilization, it will have a pH of 7.3 ± 0.2. Filter, if necessary to clarify, dispense into suitable containers, and sterilize using a validated filtration process. Store at a temperature between 2° and 25° in a sterile well-closed container, unless it is intended for immediate use.

Soybean–Casein Digest Medium is to be incubated at 22.5 ± 2.5°.

◆Media for Penicillins or Cephalosporins

Where sterility test media are to be used in the *Direct Inoculation of the Culture Medium* method under *Test for Sterility of the Product to be Examined*, modify the preparation of *Fluid Thioglycollate Medium* and the *Soybean–Casein Digest Medium* as follows. To the containers of each medium, transfer aseptically a quantity of β-lactamase sufficient to inactivate the amount of antibiotic in the specimen under test. Determine the quantity of β-lactamase required to inactivate the antibiotic by using a β-lactamase preparation that has been assayed previously for its penicillin- or cephalosporin-inactivating power. [NOTE—Supplemented β-lactamase media can also be used in the membrane filtration test.]

Alternatively (in an area completely separate from that used for sterility testing), confirm that an appropriate amount of β-lactamase is incorporated into the medium, following either method under *Validation Test*, using less than 100 colony-forming units (cfu) of *Staphylococcus aureus* (see *Table 1*) as the challenge. Typical microbial growth of the inoculated culture must be observed as a confirmation that the β-lactamase concentration is appropriate.◆

Suitability Tests

The media used comply with the following tests, carried out before, or in parallel, with the test on the product to be examined.

STERILITY

Confirm the sterility of each sterilized batch of medium by incubating a portion of the media at the specified incubation temperature for 14 days. No growth of microorganisms occurs.

GROWTH PROMOTION TEST OF AEROBES, ANAEROBES, AND FUNGI

Test each lot of of ready-prepared medium and each batch of medium prepared either from dehydrated medium or from ingredients◆[1]◆. Suitable strains of microorganisms are indicated in *Table 1*.

Inoculate portions of *Fluid Thioglycollate Medium* with a small number (not more than 100 cfu) of the following microorganisms, using a separate portion of medium for each of the following species of microorganism: *Clostridium sporogenes*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus*. Inoculate portions of *Alternative Fluid Thioglycollate Medium* with a small number (not more than 100 cfu) of *Clostridium sporogenes*. Inoculate portions of *Soybean–Casein Digest Medium* with a small number (not more than 100 cfu) of the following microorganisms, using a separate portion of medium for each of the following species of microorganism: *Aspergillus niger*, *Bacillus subtilis*, and *Candida albicans*. Incubate for not more than 3 days in the case of bacteria and not more than 5 days in the case of fungi.

The media are suitable if a clearly visible growth of the microorganisms occurs.

◆STORAGE

If prepared media are stored in unsealed containers, they can be used for 1 month, provided that they are tested for growth promotion within 2 weeks of the time of use and that color indicator requirements are met. If stored in tight containers, the media can be used for 1 year, provided that they are tested for growth promotion within 3 months of the time of use and that the color indicator requirements are met.◆

◆[1] In appropriate cases, periodic testing of the different batches prepared from the same lot of dehydrated medium is acceptable.◆

Table 1. Strains of the Test Microorganisms Suitable for Use in the Growth Promotion Test and the Validation Test

Aerobic bacteria	
Staphylococcus aureus◆[1]◆	ATCC 6538, CIP 4.83, NCTC 10788, NCIMB 9518
Bacillus subtilis	ATCC 6633, CIP 52.62, NCIMB 8054
Pseudomonas aeruginosa◆[2]◆	ATCC 9027, NCIMB 8626, CIP 82.118
Anaerobic bacterium	
Clostridium sporogenes◆[3]◆	ATCC 19404, CIP 79.3, NCTC 532 or ATCC 11437
Fungi	
Candida albicans	ATCC 10231, IP 48.72, NCPF 3179
Aspergillus niger	ATCC 16404, IP 1431.83, IMI 149007

◆[1] An alternative to *Staphylococcus aureus* is *Bacillus subtilis* (ATCC 6633).◆

◆[2] An alternative microorganism is *Micrococcus luteus* (*Kocuria rhizophila*), ATCC 9341.◆

◆[3] An alternative to *Clostridium sporogenes*, when a nonspore-forming microorganism is desired, is *Bacteroides vulgatus* (ATCC 8482).◆

[NOTE—Seed-lot culture maintenance techniques (seed-lot systems) are used so that the viable microorganisms used for inoculation are not more than five passages removed from the original master seed lot.]

◆DILUTING AND RINSING FLUIDS FOR MEMBRANE FILTRATION

Fluid A

PREPARATION

Dissolve 1 g of peptic digest of animal tissue in water to make 1 liter, filter or centrifuge to clarify, if necessary, and adjust to a pH of 7.1 ± 0.2. Dispense into containers, and sterilize using a validated process.

PREPARATION FOR PENICILLINS OR CEPHALOSPORINS

Aseptically add to the above *Preparation*, if necessary, a quantity of sterile β-lactamase sufficient to inactivate any residual antibiotic activity on the membranes after the solution of the test specimen has been filtered (see *Media for Penicillins or Cephalosporins*).

Fluid D

To each liter of *Fluid A* add 1 mL of polysorbate 80, adjust to a pH of 7.1 ± 0.2, dispense into containers, and sterilize using a validated process. Use this fluid for articles containing lecithin or oil, or for devices labeled as "sterile pathway."

Fluid K

Dissolve 5.0 g of peptic digest of animal tissue, 3.0 g of beef extract, and 10.0 g of polysorbate 80 in water to make 1 liter. Adjust the pH to obtain, after sterilization, a pH of 6.9 ± 0.2. Dispense into containers, and sterilize using a validated process.◆

VALIDATION TEST

Carry out a test as described below under *Test for Sterility of the Product to be Examined* using exactly the same methods, except for the following modifications.

Membrane Filtration

After transferring the content of the container or containers to be tested to the membrane, add an inoculum of a small number of viable microorganisms (not more than 100 cfu) to the final portion of sterile diluent used to rinse the filter.

Direct Inoculation

After transferring the contents of the container or containers to be tested (for catgut and other surgical sutures for veterinary use: strands) to the culture medium, add an inoculum of a small number of viable microorganisms (not more than 100 cfu) to the medium.

In both cases use the same microorganisms as those described above under *Growth Promotion Test of Aerobes, Anaerobes, and Fungi*. Perform a growth promotion test as a positive control. Incubate all the containers containing medium for not more than 5 days.

If clearly visible growth of microorganisms is obtained after the incubation, visually comparable to that in the control vessel without product, either the product possesses no antimicrobial activity under the conditions of the test or such activity has been satisfactorily eliminated. The test for sterility may then be carried out without further modification.

If clearly visible growth is not obtained in the presence of the product to be tested, visually comparable to that in the control vessels without product, the product possesses antimicrobial activity that has not been satisfactorily eliminated under the conditions of the test. Modify the conditions in order to eliminate the antimicrobial activity, and repeat the validation test.

This validation is performed (a) when the test for sterility has to be carried out on a new product; and (b) whenever there is a change in the experimental conditions of the test. The validation may be performed simultaneously with the *Test for Sterility of the Product to be Examined*.

TEST FOR STERILITY OF THE PRODUCT TO BE EXAMINED

◆Number of Articles to Be Tested

Unless otherwise specified elsewhere in this chapter or in the individual monograph, test the number of articles specified in *Table 3*. If the contents of each article are of sufficient quantity (see *Table 2*), they may be divided so that equal appropriate portions are added to each of the specified media. [NOTE—Perform sterility testing employing two or more of the specified media.] If each article does not contain sufficient quantities for each medium, use twice the number of articles indicated in *Table 3*.◆

Table 2. Minimum Quantity to be Used for Each Medium

Quantity per Container	Minimum Quantity to be Used (unless otherwise justified and authorized)
Liquids (other than anitbiotics)	
Less than 1 mL	The whole contents of each container
1–40 mL	Half the contents of each container, but not less than 1 mL
Greater than 40 mL, and not greater than 100 mL	20 mL
Greater than 100 mL	10% of the contents of the container, but not less than 20 mL
Antibiotic liquids	1 mL
Other preparations soluble in water or in isopropyl myristate	The whole contents of each container to provide not less than 200 mg
Insoluble preparations, creams, and ointments to be suspended or emulsified	Use the contents of each container to provide not less than 200 mg
Solids	
Less than 50 mg	The whole contents of each container
50 mg or more, but less than 300 mg	Half the contents of each container, but not less than 50 mg
300 mg–5 g	150 mg
Greater than 5 g	500 mg
Devices	
Catgut and other surgical sutures for veterinary use	3 sections of a strand (each 30-cm long)
◆Surgical dressing/cotton/gauze (in packages)	100 mg per package
Sutures and other individually packaged single-use material	The whole device
Other medical devices	The whole device, cut into pieces or disassembled◆

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Table 3. Minimum Number of Articles to be Tested in Relation to the Number of Articles in the Batch

Number of Items in the Batch	Minimum Number of Items to be Tested for Each Medium (unless otherwise justified and authorized)*
Parenteral preparations	
Not more than 100 containers	10% or 4 containers, whichever is the greater
More than 100 but not more than 500 containers	10 containers
More than 500 containers	2% or 20 containers, whichever is less
◆*For large-volume parenterals*	2% or 10 containers, whichever is less
Antibiotic solids	
Pharmacy bulk packages (<5 g)	20 containers
Pharmacy bulk packages (≥5 g)	6 containers
Bulks and blends	See *Bulk solid products*◆
Ophthalmic and other noninjectable preparations	
Not more than 200 containers	5% or 2 containers, whichever is the greater
More than 200 containers	10 containers
If the product is presented in the form of single-dose containers, apply the scheme shown above for preparations for parenteral use.	
Devices	
Catgut and other surgical sutures for veterinary use	2 % or 5 packages, whichever is the greater, up to a maximum total of 20 packages
◆Not more than 100 articles	10% or 4 articles, whichever is greater
More than 100, but not more than 500 articles	10 articles
More than 500 articles	2% or 20 articles, whichever is less◆
Bulk solid products	
Up to 4 containers	Each container
More than 4 containers, but not more than 50 containers	20% or 4 containers, whichever is greater
More than 50 containers	2% or 10 containers, whichever is greater

* If the contents of one container are enough to inoculate the two media, this column gives the number of containers needed for both the media together.

The test may be carried out using the technique of *Membrane Filtration* or by *Direct Inoculation of the Culture Medium* with the product to be examined. Appropriate negative controls are included. The technique of membrane filtration is used whenever the nature of the product permits; that is, for filterable aqueous preparations, for alcoholic or oily preparations, and for preparations miscible with, or soluble in, aqueous or oily solvents, provided these solvents do not have an antimicrobial effect in the conditions of the test.

Membrane Filtration

Use membrane filters having a nominal pore size not greater than 0.45 µm whose effectiveness to retain microorganisms has been established. Cellulose nitrate filters, for example, are used for aqueous, oily, and weakly alcoholic solutions; and cellulose acetate filters, for example, are used for strongly alcoholic solutions. Specially adapted filters may be needed for certain products, e.g. for antibiotics.

The technique described below assumes that membranes about 50 mm in diameter will be used. If filters of a different diameter are used, the volumes of the dilutions and the washings should be adjusted accordingly. The filtration apparatus and membrane are sterilized by appropriate means. The apparatus is designed so that the solution to be examined can be introduced and filtered under aseptic conditions: it permits the aseptic removal of the membrane for transfer to the medium, or it is suitable for carrying out the incubation after adding the medium to the apparatus itself.

AQUEOUS SOLUTIONS

If appropriate, transfer a small quantity of a suitable, sterile diluent such as ◆*Fluid A* (see *Diluting and Rinsing Fluids for Membrane Filtration*)◆ onto the membrane in the apparatus and filter. The diluent may contain suitable neutralizing substances and/or appropriate inactivating substances, for example, in the case of antibiotics.

Transfer the contents of the container or containers to be tested to the membrane or membranes, if necessary, after diluting to the volume used in the *Validation Test* with the chosen sterile diluent, but using not less than the quantities of the product to be examined prescribed in *Tables 2* and *3*. Filter immediately. If the product has antimicrobial properties, wash the membrane not less than three times by filtering through it each time the volume of the chosen sterile diluent used in the *Validation Test*. Do not exceed a washing cycle of 5 times 200 mL, even if during validation it has been demonstrated that such a cycle does not fully eliminate the antimicrobial activity. Transfer the whole membrane to the culture medium or cut it aseptically into two equal parts, and transfer one half to each of two suitable media. Use the same volume of each medium as in the *Validation Test*. Alternatively, transfer the medium onto the membrane in the apparatus. Incubate the media for not less than 14 days.

SOLUBLE SOLIDS (OTHER THAN ANTIBIOTICS)

Use for each medium not less than the quantity prescribed in *Tables 2* and *3* of the product dissolved in a suitable solvent, such as ◆*Fluid A* (*Diluting and Rinsing Fluids for Membrane Filtration*),◆ and proceed with the test as described above for *Aqueous Solutions* using a membrane appropriate to the chosen solvent.

OILS AND OILY SOLUTIONS

Use for each medium not less than the quantity of the product prescribed in *Tables 2* and *3*. Oils and oily solutions of sufficiently low viscosity may be filtered without dilution through a dry membrane. Viscous oils may be diluted as necessary with a suitable sterile diluent such as isopropyl myristate shown not to have antimicrobial activity in the conditions of the test. Allow the oil to penetrate the membrane by its own weight, and then filter, applying the pressure or suction gradually. Wash the membrane at least three times by filtering through it each time about 100 mL of a suitable sterile solution such as ◆*Fluid A* (see *Diluting and Rinsing Fluids for Membrane Filtration*)◆ containing a suitable emulsifying agent at a concentration shown to be appropriate in the validation of the test, for example polysorbate 80 at a concentration of 10 g per liter ◆(*Fluid K*)◆. Transfer the membrane or membranes to the culture medium or media, or vice versa, as described above for *Aqueous Solutions*, and incubate at the same temperatures and for the same times.

OINTMENTS AND CREAMS

Use for each medium not less than the quantities of the product prescribed in *Tables 2* and *3*. Ointments in a fatty base and emulsions of the water-in-oil type may be diluted to 1% in isopropyl myristate as described above, by heating, if necessary, to not more than 40°. In exceptional cases it may be necessary to heat to not more than 44°. Filter as rapidly as possible and proceed as described above for *Oils and Oily Solutions*.

◆PREFILLED SYRINGES

For prefilled syringes without attached sterile needles, expel the contents of each syringe into one or two separate membrane filter funnels or into separate pooling vessels prior to transfer. If a separate sterile needle is attached, directly expel the syringe contents as indicated above, and proceed as directed for *Aqueous Solutions*. Test the sterility of the needle, using *Direct Inoculation* under *Validation Test*.

SOLIDS FOR INJECTION OTHER THAN ANTIBIOTICS

Constitute the test articles as directed on the label, and proceed as directed for *Aqueous Solutions* or *Oils and Oily Solutions*, whichever applies. [NOTE—If necessary, excess diluent can be added to aid in the constitution and filtration of the constituted test article.]

ANTIBIOTIC SOLIDS FOR INJECTION

Pharmacy Bulk Packages, < 5 g—From each of 20 containers, aseptically transfer about 300 mg of solids, into a sterile 500-mL conical flask, dissolve in about 200 mL of *Fluid A* (see *Diluting and Rinsing Fluids for Membrane Filtration*), and mix; or constitute, as directed in the labeling, each of 20 containers and transfer a quantity of liquid or suspension, equivalent to about 300 mg of solids, into a sterile 500-mL conical flask, dissolve in about 200 mL of *Fluid A*, and mix. Proceed as directed for *Aqueous Solutions* or *Oils and Oily Solutions*, whichever applies.

Pharmacy Bulk Packages, ≥5 g—From each of 6 containers, aseptically transfer about 1 g of solids into a sterile 500-mL conical flask, dissolve in about 200 mL of *Fluid A*, and mix; or constitute, as directed in the labeling, each of 6 containers and transfer a quantity of liquid, equivalent to about 1 g of solids, into a sterile 500-mL conical flask, dissolve in about 200 mL of *Fluid A*, and mix. Proceed as directed for *Aqueous Solutions*.

ANTIBIOTIC SOLIDS, BULKS, AND BLENDS

Aseptically remove a sufficient quantity of solids from the appropriate amount of containers (see *Table 2*), mix to obtain a composite, equivalent to about 6 g of solids, and transfer to a sterile 500-mL conical flask. Dissolve in about 200 mL of *Fluid A*, and mix. Proceed as directed for *Aqueous Solutions*.

STERILE AEROSOL PRODUCTS

For fluid products in pressurized aerosol form, freeze the containers in an alcohol-dry ice mixture at least at –20° for about 1 hour. If feasible, allow the propellant to escape before aseptically opening the container, and transfer the contents to a sterile pooling vessel. Add 100 mL of *Fluid D* to the pooling vessel, and mix gently. Proceed as directed for *Aqueous Solutions* or *Oils and Oily Solutions*, whichever applies.

DEVICES WITH PATHWAYS LABELED STERILE

Aseptically pass not less than 10 pathway volumes of *Fluid D* through each device tested. Collect the fluids in an appropriate sterile vessel, and proceed as directed for *Aqueous Solutions* or *Oils and Oily Solutions*, whichever applies.

In the case of sterile, empty syringes, draw sterile diluent into the barrel through the sterile needle, if attached, or through a sterile needle attached for the purpose of the test, and express the contents into a sterile pooling vessel. Proceed as directed above.◆

Direct Inoculation of the Culture Medium

Transfer the quantity of the preparation to be examined prescribed in *Tables 2* and *3* directly into the culture medium so that the volume of the product is not more than 10% of the volume of the medium, unless otherwise prescribed.

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If the product to be examined has antimicrobial activity, carry out the test after neutralizing this with a suitable neutralizing substance or by dilution in a sufficient quantity of culture medium. When it is necessary to use a large volume of the product, it may be preferable to use a concentrated culture medium prepared in such a way that it takes into account the subsequent dilution. Where appropriate, the concentrated medium may be added directly to the product in its container.

OILY LIQUIDS

Use media to which have been added a suitable emulsifying agent at a concentration shown to be appropriate in the validation of the test, for example polysorbate 80 at a concentration of 10 g per liter.

OINTMENTS AND CREAMS

Prepare by diluting to about 1 in 10 by emulsifying with the chosen emulsifying agent in a suitable sterile diluent such as ◆*Fluid A* (see *Diluting and Rinsing Fluids for Membrane Filtration*).◆ Transfer the diluted product to a medium not containing an emulsifying agent.

Incubate the inoculated media for not less than 14 days. Observe the cultures several times during the incubation period. Shake cultures containing oily products gently each day. However, when thioglycollate medium or other similar medium is used for the detection of anaerobic microorganisms, keep shaking or mixing to a minimum in order to maintain anaerobic conditions.

CATGUT AND OTHER SURGICAL SUTURES FOR VETERINARIAN USE

Use for each medium not less than the quantities of the product prescribed in *Tables 2* and *3*. Open the sealed package using aseptic precautions, and remove three sections of the strand for each culture medium. Carry out the test on three sections, each 30-cm long, which have been cut off from the beginning, the center, and the end of the strand. Use whole strands from freshly opened cassette packs. Transfer each section of the strand to the selected medium. Use sufficient medium to cover adequately the material to be tested (20 mL to 150 mL).

◆SOLIDS

Transfer a quantity of the product in the form of a dry solid (or prepare a suspension of the product by adding sterile diluent to the immediate container), corresponding to not less than the quantity indicated in *Tables 2* and *3*. Transfer the material so obtained to 200 mL of *Fluid Thioglycollate Medium*, and mix. Similarly, transfer the same quantity to 200 mL of *Soybean–Casein Digest Medium*, and mix. Proceed as directed above.

PURIFIED COTTON, GAUZE, SURGICAL DRESSINGS, AND RELATED ARTICLES

From each package of cotton, rolled gauze bandage, or large surgical dressings being tested, aseptically remove two or more portions of 100- to 500-mg each from the innermost part of the sample. From individually packaged, single-use materials, aseptically remove the entire article. Immerse the portions or article in each medium, and proceed as directed above.

STERILE DEVICES

Articles can be immersed intact or disassembled. To ensure that device pathways are also in contact with the media, immerse the appropriate number of units per medium in a volume of medium sufficient to immerse the device completely, and proceed as directed above. For extremely large devices, immerse those portions of the device that are to come into contact with the patient in a volume of medium sufficient to achieve complete immersion of those portions.

For catheters where the inside lumen and outside are required to be sterile, either cut them into pieces such that the medium is in contact with the entire lumen or fill the lumen with medium, and then immerse the intact unit.◆

OBSERVATION AND INTERPRETATION OF RESULTS

At intervals during the incubation period and at its conclusion, examine the media for macroscopic evidence of microbial growth. If the material being tested renders the medium turbid so that the presence or absence of microbial growth cannot be readily determined by visual examination, 14 days after the beginning of incubation transfer portions (each not less than 1 mL) of the medium to fresh vessels of the same medium, and then incubate the original and transfer vessels for not less than 4 days.

If no evidence of microbial growth is found, the product to be examined complies with the test for sterility. If evidence of microbial growth is found, the product to be examined does not comply with the test for sterility, unless it can be clearly demonstrated that the test was invalid for causes unrelated to the product to be examined. The test may be considered invalid only if one or more of the following conditions are fulfilled:

a. The data of the microbiological monitoring of the sterility testing facility show a fault.
b. A review of the testing procedure used during the test in question reveals a fault.
c. Microbial growth is found in the negative controls.
d. After determination of the identity of the microorganisms isolated from the test, the growth of this species (or these species) may be ascribed unequivocally to faults with respect to the material and or the technique used in conducting the sterility test procedure.

If the test is declared to be invalid, it is repeated with the same number of units as in the original test. If no evidence of microbial growth is found in the repeat test, the product examined complies with the test for sterility. If microbial growth is found in the repeat test, the product examined does not comply with the test for sterility.

APPLICATION OF THE TEST TO PARENTERAL PREPARATIONS, OPHTHALMIC, AND OTHER NONINJECTABLE PREPARATIONS REQUIRED TO COMPLY WITH THE TEST FOR STERILITY

When using the technique of membrane filtration, use, whenever possible, the whole contents of the container, but not less than the quantities indicated in *Tables 2* and *3*, diluting where necessary to about 100 mL with a suitable sterile solution, such as ◆*Fluid A* (see *Diluting and Rinsing Fluids for Membrane Filtration*).◆

When using the technique of direct inoculation of media, use the quantities shown in *Tables 2* and *3*, unless otherwise justified and authorized. The tests for bacterial and fungal sterility are carried out on the same sample of the product to be examined. When the volume or the quantity in a single container is insufficient to carry out the tests, the contents of two or more containers are used to inoculate the different media.

(Official January 1, 2004)●4

●⟨797⟩ PHARMACEUTICAL COMPOUNDING—STERILE PREPARATIONS●4

Change to read:

•INTRODUCTION

This chapter provides procedures and requirements for compounding sterile preparations. Sterile compounding differs from nonsterile compounding (see *Pharmaceutical Compounding — Nonsterile Preparations* ⟨795⟩ and *Good Compounding Practices* ⟨1075⟩) primarily by requiring a test for sterility. Sterile compounding also requires cleaner facilities; specific training and testing of personnel in principles and practices of aseptic manipulations; air quality evaluation and maintenance; and sound knowledge of sterilization and solution stability principles and practices. Greater care is required for aqueous injections that are compounded sterile preparations (CSPs)—the most common CSPs used in therapy. Aqueous injections for administration into the vascular and central nervous systems pose the greatest risk of harm to patients if there are issues of nonsterility and large errors in ingredients.

The intent of this chapter is to prevent harm and fatality to patients that could result from microbial contamination (nonsterility), excessive bacterial endotoxins, large content errors in the strength of correct ingredients, and incorrect ingredients in CSPs. The quality control and testing for CSPs in this chapter are appropriate and necessary. The content of this chapter applies to health care institutions, pharmacies, physician practice facilities, and other facilities in which CSPs are prepared, stored, and dispensed. For the purposes of this chapter, CSPs include any of the following:

a. Preparations prepared according to the maufacturer's labeled instructions and other manipulations when manufacturing sterile products that expose the original contents to potential contamination.
b. Preparations containing nonsterile ingredients or employing nonsterile components and devices that must be sterilized before administration.
c. Biologics, diagnostics, drugs, nutrients, and radiopharmaceuticals that possess either of the above two characteristics, and which include, but are not limited to, baths and soaks for live organs and tissues, implants, inhalations, injections, powders for injection, irrigations, metered sprays, and ophthalmic and otic preparations.

The sections in this chapter are organized to facilitate practitioners' understanding of the fundamental accuracy and quality practices of CSPs. They provide a foundation for the development and implementation of essential procedures for the safe preparation of CSP's in the three risk levels, which are classified according to the potential for microbial, chemical, and physical contamination. The chapter is divided into the following main sections:

- Responsibilities of all compounding personnel
- The basis for the classification of a CSP into a low-, medium-, and high-risk level, with examples of CSPs and their quality assurance practices in each of these risk levels
- Verification of compounding accuracy and sterilization
- Personnel training and evaluation in aseptic manipulation skills, including representative sterile microbial culture medium transfer and fill challenges
- Environmental quality and control during the processing of CSPs
- Equipment used in the preparation of CSPs
- Verification of automated compounding devices for parenteral nutrition compounding
- Finished preparation release checks and tests
- Storage and beyond-use dating
- Maintaining product quality and control after CSPs leave the compounding facility, including education and training of personnel
- Packing, handling, storage, and transport of CSPs
- Patient or caregiver training
- Patient monitoring and adverse events reporting
- A quality assurance program for CSPs

It is the ultimate responsibility of all personnel who prepare CSPs to understand these fundamental practices and precautions, to develop and implement appropriate procedures, and to continually evaluate these procedures and the quality of final CSPs to prevent harm and fatality to patients who are treated with CSPs.●4

Delete the following:

•RESPONSIBILITY OF THE DISPENSING PHARMACIST

A pharmacist dispensing any SP is responsible for ensuring that the product has been prepared, labeled, controlled, stored, dispensed, and distributed properly. This includes the responsibility for ensuring that the SP is kept under appropriate controlled conditions at the location of use and that it is administered properly through adequate labeling and verbal or written instructions. The dispensing pharmacist is also responsible for ensuring that the SP retains its quality attributes within acceptable limits through a written quality assurance program. This program should ensure that for the entire labeled life of the product, or until manipulated by the clinician, patient, or caregiver, the potency, pH, sterility, freedom from pyrogens, particulate limits, container integrity, appearance, and other qualities or characteristics that the SP is expected to have do exist. The quality assurance program should encompass every SP under the pharmacy's control and includes all phases of its preparation, distribution, storage, administration, and use. The dispensing pharmacy should employ proper analytical testing, where appropriate, to ensure the microbiological, chemical, and physical quality of all SPs. These responsibilities apply equally to commercially available injectable drug products that are dispensed to patients without compounding or other manipulation and to SPs that

have been repackaged, reconstituted, diluted, admixed, blended, or otherwise manipulated (collectively referred to as ''Compounded'') in any way prior to dispensing. The pharmacist is responsible for ensuring that quality is built into the preparation of products, with key factors including at least the following general principles:

(1) Personnel are capable and qualified to perform their assigned duties.
(2) Ingredients usedin compounding have their expected identity, quality, and purity.
(3) Critical processes are validated to ensure that procedures, when used, will consistently result in the expected qualities in the finished product.
(4) The production environment is suitable for its intended purpose (addressing such matters as environmental cleanliness, control, monitoring, and the setting of action limits, as appropriate).
(5) Appropriate release checks or testing procedures are performed to ensure that finished products have their expected potency, purity, quality, and characteristics at the time of release.
(6) Appropriate stability evaluation is performed or determined from the literature for establishing reliable beyond-use dating to ensure that finished products have their expected potency, purity, quality, and characteristics at least until the labeled beyond-use date.
(7) There is assurance that processes are always carried out as intended or specified and are under control.
(8) Preparation conditions and procedures are adequate for preventing mixups.
(9) There are adequate procedures and records for investigating and correcting failures or problems in preparation, testing, or in the product itself.
(10) There is adequate separation of quality control functions and decisions from those of production.

Emphasis in this chapter is placed upon the quality and the control of the processes utilized, personnel performance, and the environmental conditions under which the processes are performed. Other factors, such as testing and stability, are addressed to the extent necessary for the limited quantities of products with relatively short beyond-use dating periods normally associated with home care pharmacy practice. This chapter is not intended to address issues concerning the manufacture of sterile drug products.●4

Add the following:

•RESPONSIBILITY OF COMPOUNDING PERSONNEL

Compounding personnel are responsible for ensuring that CSPs are accurately identified, measured, diluted, and mixed; and are correctly purified, sterilized, packaged, sealed, labeled, stored, dispensed, and distributed. These performance responsibilities include maintaining appropriate cleanliness conditions and providing labeling and supplementary instructions for the proper clinical administration of CSPs.

Compounding supervisors shall ensure through either direct measurement or appropriate information sources that specific CSPs maintain their labeled strength within monograph limits for USP articles, or within 10% if not specified, until their beyond-use dates. All CSPs are prepared in a manner that maintains sterility and minimizes the introduction of particulate matter.

A written quality assurance procedure includes the following in-process checks that are applied, as is appropriate, to specific CSPs: accuracy and precision of measuring and weighing; the requirement for sterility; methods of sterilization and purification; safe limits and ranges for strength of ingredients, bacterial endotoxins, particulate matter, and pH; labeling accuracy and completeness; beyond-use date assignment; and packaging and storage requirements. The dispenser shall, when appropriate and practicable, obtain and evaluate results of testing for identity, strength, purity, and sterility before a CSP is dispensed. Qualified licensed health care professionals who supervise compounding and dispensing of CSPs shall ensure that the following objectives are achieved.

1. Compounding personnel are adequately skilled, educated, instructed, and trained to correctly perform and document the following activities in their sterile compounding duties:
   a. Perform antiseptic hand cleansing and disinfection of nonsterile compounding surfaces;
   b. Select and appropriately don protective gloves, goggles, gowns, masks, and hair and shoe covers;
   c. Use laminar flow clean-air hoods, barrier isolators, and other contamination control devices that are appropriate for the risk level;
   d. Identify, weigh, and measure ingredients; and
   e. Manipulate sterile products aseptically, sterilize high-risk level CSPs, and label and quality inspect CSPs.
2. Ingredients have their correct identity, quality, and purity.
3. Opened or partially used packages of ingredients for subsequent use in CSPs are properly stored under restricted access conditions in the compounding facility. Such packages cannot be used when visual inspection detects unauthorized breaks in the container, closure, and seal; when the contents do not possess the expected appearance, aroma, and texture; when the contents do not pass identification tests specified by the compounding facility; and when either the beyond-use or expiration date has been exceeded.
4. To minimize the generation of bacterial endotoxins, water-containing CSPs that are nonsterile during any phase of the compounding procedure are sterilized within 6 hours after completing the preparation.
5. Sterilization methods achieve sterility of CSPs while maintaining the labeled strength of active ingredients and the physical integrity of packaging.
6. Measuring, mixing, sterilizing, and purifying devices are clean, appropriately accurate, and effective for their intended uses.
7. Potential harm from added substances and differences in rate and extent of bioavailability of active ingredients for other than oral route of administration are carefully evaluated before such CSPs are dispensed and administered.
8. Packaging selected for CSPs is appropriate to preserve the sterility and strength until the beyond-use date.
9. While being used, the compounding environment maintains the sterility or the presterilization purity, whichever is appropriate, of the CSP.
10. Labels on CSPs list the names and amounts or concentrations of all ingredients. Before being dispensed, and or administered, the clarity of solutions are visually confirmed; also the identity and amounts of ingredients, procedures to prepare and sterilize CSPs, and specific release criteria are reviewed to assure their accuracy and completeness.
11. Beyond-use dates are assigned based on direct testing or extrapolation from reliable literature sources and other documentation (see *Stability Criteria* and *Beyond-Use Dating* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).
12. Procedures for measuring, mixing, dilution, purification, sterilization, packaging, and labeling conform to the correct sequence and quality established for the specified CSP.
13. Deficiencies in compounding, labeling, packaging, and quality testing and inspection can be rapidly identified and corrected.
14. When time and personnel availability so permit, compounding manipulations and procedures are separated from post-compounding quality inspection and review before CSPs are dispensed and administered.

This chapter emphasizes the need to maintain high standards for the quality and control of processes, components, and environments; and for the skill and knowledge of personnel who prepare CSPs. The rigor of in-process quality-control checks and of post-compounding quality inspection and testing increases corresponding to the potential hazard of the route of administration. For example, nonsterility, excessive bacterial endotoxin contamination, large errors in strength of correct ingredients, and incorrect ingredients in CSPs are potentially more dangerous to patients when the CSPs are administered into the vascular and central nervous systems than when administered by most other routes.●4

Delete the following:

•RISK LEVELS

With reference to the microbiological quality (i.e., sterility) of the finished drug product, an SP, in general, is compounded under either relatively *low-risk* or *high-risk* conditions, as determined by the potential for the introduction of microbial contamination. This contamination may result from the use of nonsterile components; novel, complex, or prolonged aseptic processes; or open exposure of the drug product or product containment devices to the atmosphere. In addition, long storage time between compounding and initiation of administration may affect the microbiological quality of the finished drug product.

The characteristics itemized below to distinguish between the high-risk and low-risk levels are intended to provide conceptual guidance and are not intended to be prescriptive. The pharmacist is expected to exercise professional judgment on a case-by-case basis when determining the risk level that would be appropriate for a particular process.

Low-Risk

An SP is considered to be aseptically processed under low-risk conditions when all of the following conditions prevail:

(1) The finished product is compounded with commercially available, sterile drug products.
(2) Compounding involves only basic, and relatively few, aseptic manipulations that are promptly executed.
(3) ''Closed system'' transfers are used: the container-closure system remains essentially intact throughout the aseptic process, compromised only by the penetration of a sterile, pyrogen-free needle or cannula through the designated stopper or port to affect transfer, withdrawal, or delivery in accordance with the labeled instructions for the pertinent, commercially available devices. Opened ampuls should be regarded as if they are closed systems for purposes of this chapter.

Examples of low-risk processes include the following:

(1) Transferring sterile drug products from vials or ampuls into sterile final containers using a sterile needle and syringe.
(2) Transferring sterile drug products into sterile elastomeric infusion containers with the aid of a mechanical pump and an appropriate sterile transfer tubing device, with or without the subsequent addition of sterile drug products to the infusion container with a sterile needle and syringe.
(3) Compounding sterile nutritional solutions by combining *Dextrose Injection* and *Amino Acids Injection* via gravity transfer into sterile empty containers, with or without the subsequent addition of sterile drug products to the final container with a sterile needle and syringe.

High-Risk

Category I—A high-risk SP may fall into either of two subclassifications. High-risk SPs in *Category I* are those prepared from commercially available, sterile components where one or more of the following conditions prevail:

(1) Compounding involves the intermediate closed system pooling of sterile drug products. Pooling of additives is defined as a higher risk process than performing multiple single additives because contamination of the pool could result in contamination of units filled from the pool, thus potentially causing epidemic infection.
(2) Compounding includes complex and/or numerous aseptic manipulations executed over a prolonged period.
(3) An individual finished product is administered as a multi-day infusion via a portable pump or reservoir.

Examples of high-risk category I processes include the following:

(1) Compounding sterile nutritional solutions using an automated compounding device involving repeated attachment of fluid containers to proximal openings of the compounder tubing set and of empty final containers to the distal opening. The process concludes with the transfer of additives into the filled final container from individual drug product containers or from a pooled additive solution.
(2) Preparing ambulatory pump reservoirs by adding more than one drug product with the evacuation of air from the reservoir prior to dispensing.
(3) Preparing ambulatory pump reservoirs for multi-day (i.e., ambient temperature) administration.

Category II—High-risk SPs in *Category II* are those involving either of the following:

(1) A nonsterile drug substance or an injectable drug product prepared in-house from a nonsterile substance is used to compound the SP.
(2) ''Open systems'' are used, for example, when combining ingredients in a nonsealed reservoir before filling or when fluid passes through the atmosphere during a fill-seal operation.

Examples of high-risk category II processes include the following:

(1) Compounding injectable morphine solutions from nonsterile morphine substance and suitable vehicles.
(2) Compounding sterile nutritional solutions from nonsterile ingredients with initial mixing in a nonsealed or nonsterile reservoir.●4

Add the following:

•CSP MICROBIAL CONTAMINATION RISK LEVELS

The appropriate risk level—low, medium, or high—is assigned according to the corresponding probability of contaminating a CSP with (1) microbial contamination (microbial organisms, spores, and endotoxins) and (2) chemical and physical contamination (foreign chemicals and physical matter). Potential sources of contamination include, but are not limited to, solid and liquid matter from compounding personnel and objects; nonsterile components employed and incorporated before terminal sterilization; inappropriate conditions within the restricted compounding environment; prolonged presterilization procedures with aqueous preparations; and nonsterile dosage forms used to compound CSPs.

The characteristics described below for low-risk, medium-risk, and high-risk CSPs are intended as a guide to the breadth and depth of care necessary in compounding, but they are neither exhaustive nor prescriptive. The licensed health care professionals who super-

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vise compounding are responsible for determining the procedural and environmental quality practices and attributes that are necessary for the risk level they assign to specific CSPs.

These risk levels apply to the quality of CSPs immediately after the final aseptic mixing or filling or immediately after the final sterilization, unless precluded by the specific characteristics of the preparation, such as lipid-based emulsions where administration must be completed within 12 hours of preparation. Upon subsequent storage and shipping of freshly finished CSPs, an increase in the risks of chemical degradation of ingredients, contamination from physical damage to packaging, and permeability of plastic and elastomeric packaging is expected. In such cases, compounding personnel consider the potential additional risks to the integrity of CSPs when assigning beyond-use dates. The pre-administration exposure duration and temperature limits specified in the following low-risk, medium-risk, and high-risk level sections apply in the absence of direct testing results or appropriate information sources that justify different limits for specific CSPs. For a summary of the criteria according to risk levels, please see the *Appendix*.

Low-Risk Level CSPs

CSPs compounded under all of the following conditions are at a low risk of contamination.

Low-Risk Conditions—

1. The CSPs are compounded with aseptic manipulations entirely within ISO Class 5 (see *Table 1*) or better air quality using only sterile ingredients, products, components, and devices.
2. The compounding involves only transfer, measuring, and mixing manipulations with closed or sealed packaging systems that are performed promptly and attentively.
3. Manipulations are limited to aseptically opening ampuls, penetrating sterile stoppers on vials with sterile needles and syringes, and transferring sterile liquids in sterile syringes to sterile administration devices and packages of other sterile products.
4. For a low-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 48 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 14 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20° or colder.

Examples of Low-Risk Compounding—

1. Single transfers of sterile dosage forms from ampuls, bottles, bags, and vials using sterile syringes with sterile needles, other administration devices, and other sterile containers. The contents of ampuls require sterile filtration to remove any glass particles.
2. Manually measuring and mixing no more than three manufactured products to compound drug admixtures and nutritional solutions.

Quality Assurance—

Quality assurance practices include, but are not limited to, the following:

1. Routine disinfection and air quality testing of the direct compounding environment to minimize microbial surface contamination and maintain ISO Class 5 air quality (see *Table 1*).
2. Visual confirmation that compounding personnel are properly donning and wearing appropriate items and types of protective garments and goggles.
3. Review of all orders and packages of ingredients to assure the correct identity and amounts of ingredients were compounded.
4. Visual inspection of CSPs to ensure the absence of particulate matter in solutions, the absence of leakage from vials and bags, and the accuracy and thoroughness of labeling.

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed at least annually by each person authorized to compound in a low-risk level under conditions that closely simulate the most challenging or stressful conditions encountered during compounding of low-risk level CSPs. Once begun, this test is completed without interruption. Within an ISO Class 5 air quality environment, (see *Table 1*) three sets of four 5-mL aliquots of sterile Soybean–Casein Digest Medium are transferred with the same sterile 10-mL syringe and vented needle combination into separate sealed empty sterile 30-mL clear vials (i.e., four 5-mL aliquots into each of three 30-mL vials). Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials, then the vials are incubated as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

Medium-Risk Level CSPs

When CSPs are compounded aseptically under *Low-Risk Conditions*, and one or more of the following conditions exists, such CSPs are at a medium risk of contamination.

Medium-Risk Conditions—

1. Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple occasions.
2. The compounding process includes complex aseptic manipulations other than the single-volume transfer.
3. The compounding process requires unusually long duration, such as that required to complete dissolution or homogeneous mixing.
4. The sterile CSPs do not contain broad-spectrum bacteriostatic substances, and they are administered over several days (e.g., an externally worn or implanted infusion device).
5. For a medium-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 30 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 7 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20° or colder.

Examples of Medium-Risk Compounding—

1. Compounding of total parenteral nutrition fluids using manual or automated devices during which there are multiple injections, detachments, and attachments of nutrient source products to the device or machine to deliver all nutritional components to a final sterile container.
2. Filling of reservoirs of injection and infusion devices with multiple sterile drug products and evacuation of air from those reservoirs before the filled device is dispensed.
3. Filling of reservoirs of injection and infusion devices with volumes of sterile drug solutions that will be administered over several days at ambient temperatures between 25° and 40°.
4. Transfer of volumes from multiple ampuls or vials into a single, final sterile container or product.

Quality Assurance—Quality assurance procedures for medium-risk level CSPs include all those for low-risk level CSPs, as well as a more challenging media-fill test passed annually, or more frequently.

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed under conditions that closely simulate the most challenging or stressful conditions encountered during compounding. This test is completed without interruption within an ISO Class 5 air quality environment (see *Table 1*). Six 100-mL aliquots of sterile Soybean–Casein Digest Medium are aseptically transferred by gravity through separate tubing sets into separate evacuated sterile containers. The six containers are then arranged as three pairs, and a sterile 10-mL syringe and 18-gauge needle combination is used to exchange two 5-mL aliquots of medium from one container to the other container in the pair. For example, after a 5-mL aliquot from the first container is added to the second container in the pair, the second container is agitated for 10 seconds, then a 5-mL aliquot is removed and returned to the first container in the pair. The first container is then agitated for 10 seconds, and the next 5-mL aliquot is transferred from it back to the second container in the pair. Following the two 5-mL aliquot exchanges in each pair of containers, a 5-mL aliquot of medium from each container is aseptically injected into a sealed empty sterile 10-mL clear vial using a sterile 10-mL syringe and vented needle. Sterile adhesive seals are aseptically affixed to the rubber closures on the three filled vials, then the vials are incubated as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.

High-Risk Level CSPs

CSPs compounded under any of the following conditions are either contaminated or at a high risk to become contaminated with infectious microorganisms.

High-Risk Conditions—

1. Nonsterile ingredients, including manufactured products for routes of administration—other than those listed under *c.* in the *Introduction*—are incorporated or a nonsterile device is employed before terminal sterilization.
2. Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see *Table 1*). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.
3. Nonsterile preparations are exposed for at least 6 hours before being sterilized.
4. It is assumed, and not verified by examination of labeling and documentation from suppliers or by direct determination, that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients (see *Ingredient Selection* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).
5. For a high-risk preparation, in the absence of passing a sterility test, the storage periods cannot exceed the following time periods: before administration, the CSPs are properly stored and are exposed for not more than 24 hours at controlled room temperature (see *General Notices and Requirements*), for not more than 3 days at a cold temperature (see *General Notices and Requirements*), and for 45 days in solid frozen state at –20° or colder.

All nonsterile measuring, mixing, and purifying devices are rinsed thoroughly with sterile, pyrogen-free water, and then thoroughly drained or dried immediately before use for high-risk compounding. All high-risk CSP solutions subjected to terminal steam sterilization are passed through a filter with a nominal porosity not larger than 1.2 µm preceding or during filling into their final containers. Sterilization of high-risk level CSPs by filtration is conducted entirely with an ISO Class 5 or superior air quality environment (see *Table 1*).

Examples of High-Risk Compounding—

1. Dissolving nonsterile bulk drug and nutrient powders to make solutions, which will be terminally sterilized.
2. Sterile ingredients, components, devices, and mixtures are exposed to air quality inferior to ISO Class 5 (see *Table 1*). This includes storage in environments inferior to ISO Class 5 of opened or partially used packages of manufactured sterile products that lack antimicrobial preservatives.
3. Measuring and mixing sterile ingredients in nonsterile devices before sterilization is performed.
4. Assuming, without appropriate evidence or direct determination, that packages of bulk ingredients contain at least 95% by weight of their active chemical moiety and have not been contaminated or adulterated between uses.

Quality Assurance—Quality assurance procedures for high-risk level CSPs include all those for low-risk level CSPs. In addition, a media-fill test that represents high-risk level compounding is performed semi-annually by each person authorized to compound high-risk level CSPs.

Example of a Media-Fill Test Procedure—This, or an equivalent test, is performed under conditions that closely simulate the most challenging or stressful conditions encountered when compounding high-risk level CSPs. This test is completed without interruption in the following sequence:

1. Dissolve 3 g of nonsterile commercially available Soybean–Casein Digest Medium in 100 mL of nonbacteriostatic water to make a 3% solution.
2. Draw 25 mL of the medium into each of three 30-mL sterile syringes. Transfer 5 mL from each syringe into separate sterile 10-mL vials. These vials are the controls, and they generate exponential microbial growth, indicated by visible turbidity upon incubation.
3. Under aseptic conditions and using aseptic techniques, affix a sterile 0.2-µm porosity filter unit and a 20-gauge needle to each syringe. Inject the next 10 mL from each syringe into three separate 10-mL sterile vials. Repeat the process into three more vials. Label all vials, affix sterile adhesive seals to the closure of the nine vials, and incubate them at 25° to 35°. Inspect for microbial growth over 14 days as described in the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section.•4

Delete the following:

•VALIDATION

The sterilization or aseptic processing of an SP should be in accordance with properly designed and validated written procedures. The act of validation of a sterilization or aseptic process involves planned testing designed to demonstrate that microorganisms will be effectively destroyed, removed, or prevented from inadvertently being introduced by personnel or by process-related activities.

Sterilization Processes

A high-risk SP prepared from nonsterile ingredients or components should be sterilized using an appropriate sterilization process, such as filtration or heat sterilization. In general, each sterilization process should be validated to demonstrate suitability for its intended purpose and specific manner of intended uses.

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STERILIZATION BY FILTRATION

A sterilizing filtration process should be capable of removing microorganisms from the liquid SP. Commercially available presterilized filtration devices should be certified to be appropriate for human use in sterile pharmaceutical applications, have a pore size of 0.2 µm or smaller (generally recognized as a sterilizing filter), and have been lot tested for retention of *Pseudomonas diminuta* at a minimum concentration of 10^7 organisms per cm^2 under specified operating parameters. The individual devices should be tested for membrane and housing integrity, nonpyrogenicity, and extractables by the manufacturer. Such devices should be capable of sterilizing an SP (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩). Before using such devices, the pharmacist should thoroughly evaluate their suitability for the intended SP and conditions of use.

The size and configuration of filtration devices should accommodate the volume being filtered to permit complete filtration within a reasonable period of time and without clogging to the point where mid-process filter changes would be required.

Filters and associated devices and apparatus (housing, gaskets, etc.) should be physically and chemically compatible with the product to be filtered and should be capable of withstanding the temperatures, pressures, and hydrostatic stresses imposed on the system. These capabilities are to be established through appropriate product-specific testing. To establish compatibility, the pharmacy may rely on vendor certification or on definitive evidence, specific to product and filter, obtained from a critical review of the literature or from reliable unpublished research.

Validation should be established experimentally for all filtration apparatus involving assembly in the pharmacy of the membrane (filtration medium) into its housing or holder. The pharmacy may rely on vendor certification of validation for commercially available presterilized ready-to-use filter devices or for pharmacy-assembled apparatus. (The sterilization process used for pharmacy-assembled apparatus must be properly validated.) When initially selecting a commercially available, sterile, pre-assembled filter device, the pharmacist should ensure that the vendor has validated the filter for the intended conditions of use and that an adequate challenge was used (minimum concentration of 10^7 organisms *Pseudomonas diminuta* per cm^2 of filter surface). Validation should encompass the filtration apparatus and configuration, duration of filtration, filtration operating conditions (filtration rate and temperature), and the critical product formulation parameters (pH, viscosity, ionic strength, and osmolarity) used to generate the supplied data are representative of the pharmacy's product, apparatus, specified operating parameters, etc., in regard to the factors that might physically or chemically alter filter integrity, affect microbial capture mechanisms, or shrink the microorganism during filtration.

Each filter device used for product sterilization should be checked for integrity at the time of use. Integrity testing of commercially available, sterile, self-contained filter devices requiring no preuse assembly may be performed at the conclusion of the filtration process. Filter integrity test kits suitable for pharmacy use (for example, those consisting of a small gauge and a three-way stopcock assembly) are commercially available for testing the bubble point of small disk-type filters. For pharmacy-assembled apparatus, as defined above, prefiltration integrity testing is recommended in addition to postfiltration testing. Quantitative integrity testing, such as the bubble-point or forward flow tests (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩) should be used, as appropriate for larger filtration devices or when *Category II* high-risk SPs are sterilized.

Filtration should be performed in accordance with written procedures that list those filters determined to be acceptable for the various SPs to be filtered in the pharmacy or in accordance with master batch formulas that include definitive filter specifications. Filtration procedures and master batch formulas should also describe acceptable techniques for using and for checking the integrity of all listed filters. Fluid-filter compatibility must be established prior to the filtration of any SP not included in the procedure.

HEAT STERILIZATION

Terminal sterilization should be used when sterilizing *Category II* high-risk SPs. Sterilization may be accomplished in the final sealed container as a validated, controlled moist heat process (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩). In the absence of heat sterilization capabilities, or where heat labile drug products or container-closure systems preclude heat sterilization, an SP may be sterilized by filtration and aseptically processed and controlled in accordance with the standards set forth in this chapter.

Heat sterilization processes should be validated to ensure that the likelihood of survival of the most resistant microorganisms likely to constitute product bioburden is no greater than 10^{-6} under the specified operating conditions and parameters, such as sterilization time and temperature, size and nature of load, and chamber loading configuration. The validation and monitoring of heat sterilization processes should be in writing with all critical parameters specified, should be followed each time of use, and should be supervised by a pharmacist knowledgeable of the technology involved in the sterilization of drug products. Monitoring datashould be recorded properly to ensure, retrospectively, that the processes were carried out as specified and that all critical parameters were within specified limits during processing.[1] •4

Add the following:

•VERIFICATION OF COMPOUNDING ACCURACY AND STERILIZATION

The compounding procedures and sterilization methods for CSPs correspond to correctly designed and verified written documentation in the compounding facility. Verification requires planned testing designed to demonstrate effectiveness of all procedures critical to the accuracy and purity of finished CSPs. For example, sterility testing (see *Test Procedures* under *Sterility Tests* ⟨71⟩) may be applied to specimens of low- and medium-risk CSPs, and standard nonpathogenic bacterial cultures may be added to nondispensable specimens of high-risk CSPs before terminal sterilization for subsequent evaluation by sterility testing. Packaged and labeled CSPs are visually inspected for physical integrity and expected appearance, including final fill amount. To ensure that the identities and concentrations of ingredients are accurate, and in the absence of reliable observations and data to confirm and extrapolate those parameters, samples of CSPs are assayed.

Sterilization Methods

The licensed health care professionals who supervise compounding are responsible for determining that the selected sterilization method (see *Methods of Sterilization* under *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩) both sterilizes and maintains the strength, purity, quality, and packaging integrity of CSPs. The selected sterilization process is expected from experience and appropriate information sources—and, preferably, veri-

[1] PDA Technical Monograph No. 1, Validation of Steam Sterilization Cycles, 1978.

fied wherever possible—to achieve sterility in the particular CSPs. General guidelines for matching CSPs and components to appropriate sterilization methods include the following:

1. CSPs have been ascertained to remain physically and chemically stable when subjected to the selected sterilization method.
2. Glass and metal devices may be covered tightly with aluminum foil, then exposed to dry heat in an oven at a mean temperature of 250° for 2 hours to achieve sterility and depyrogenation (see *Dry-Heat Sterilization* under *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩). Such items are either used immediately or stored until use in an environment suitable for compounding low- and medium-risk CSPs.
3. Personnel ascertain from appropriate information sources that the sterile microporous membrane filter used to sterilize CSP solutions, either during compounding or administration, is chemically and physically compatible with the CSP.

STERILIZATION BY FILTRATION

Commercially available sterile filters must be approved for human-use applications in sterilizing pharmaceutical fluids. Both filters that must be sterilized before processing CSPs and those filters that are commercially available, disposable, sterile, and pyrogen-free have a nominal porosity of 0.2 µm, which includes 0.22-µm porosity. They should be certified by the manufacturer to retain at least 10^7 microorganisms of a strain of *Brevundimonas* (*Pseudomonas*) *diminuta* on each cm^2 of upstream filter surface under conditions similar to those in which the CSPs will be sterilized. In emergency situations when sterile 0.2-µm porosity membranes are not available, filters of the same composition and 0.45-µm nominal porosity may be used. Sterilizing filters with 0.2-µm and 0.45-µm nominal porosities will not remove bacterial endotoxins and viruses by physical retention.

The supervising health care professional must ensure, directly or from appropriate documentation, that the filters are chemically and physically stable at the pressure and temperature conditions to be used, and that the filters will achieve sterility and maintain prefiltration pharmaceutical quality of the specific CSP. The filter dimensions and material must permit the sterilization process to be completed rapidly without the replacement of the filter during the process. When CSPs are known to contain excessive particulate matter, a prefilter or larger porosity membrane is placed upstream from the sterilizing filter to remove gross particulate contaminants in order to maximize the efficiency of the sterilizing filter.

When filter devices are assembled from separate nonsterile components by compounding personnel, such devices shall be identified to be sterile and ascertained to be effective under relevant conditions before they are used to sterilize CSPs. For example, sterility can be identified using biological indicators (see *Biological Indicators* ⟨1035⟩). Filter units used to sterilize CSPs can also be subjected to the manufacturer's recommended integrity test, such as the bubble point test.

When commercially available sterile disposable filter devices are used, the compounding personnel may accept the written certification from suppliers that the filters retain at least 10^7 cfu, of *Brevundimonas* (*Pseudomonas*) *diminuta* on each cm^2 of filter surface. Compounding personnel must ascertain that selected filters will achieve sterilization of the particular CSPs being sterilized. Large deviations from usual or expected chemical and physical properties of CSPs may cause undetectable damage to filter integrity and shrinkage of microorganisms to sizes smaller than filter porosity.

Sterile, commercially available sterilizing filter devices for use on handheld syringes may be checked by feeling for greater resistance on the plunger when filtering air after an aqueous fluid has been filtered.

STEAM STERILIZATION

The process of thermal sterilization employing saturated steam under pressure, or autoclaving, is the preferred method to terminally sterilize aqueous preparations that have been verified to maintain their full chemical and physical stability under the conditions employed (see *Steam Sterilization* under *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩). To achieve sterility, it is necessary that all materials be exposed to steam at 121°, under a pressure of about one atmosphere or 15 psi, for the duration verified by testing to achieve sterility of the items, which is usually 20 to 60 minutes for CSPs. An allowance must be made for the time required for the material to reach 121° before the sterilization exposure duration is timed.

Items that are not directly exposed to pressurized steam may result in survival of microbial organisms and spores. Before their sterilization, plastic, glass, and metal devices are tightly wrapped in low particle shedding paper or fabrics, or sealed in envelopes that prevent poststerilization microbial penetration. Immediately before filling ampuls and vials that will be steam sterilized, solutions are passed through a filter having a porosity not larger than 1.2 µm for removal of particulate matter. Sealed containers must be able to generate steam internally; thus, stoppered and crimped empty vials must contain a small amount of moisture to generate steam.

The description of steam sterilization conditions and duration for specific CSPs is included in written documentation in the compounding facility. The effectiveness of steam sterilization is verified using appropriate biological indicators (see *Biological Indicators* ⟨1035⟩) or other confirmation methods (see *Sterilization and Sterility Assurance of Compendial Articles* ⟨1211⟩ or *Sterility Tests* ⟨71⟩).•4

Delete the following:

•ASEPTIC PROCESSING

All aseptic processing operations and configurations should be adequately established by media-fill validation.[2] Media fills should simulate as closely as possible actual aseptic operations. All manipulations, handling, environmental conditions, and other factors likely to influence the risk of process-associated contamination should be represented by the media-fill simulations. The intensity of such challenges should represent the greatest risk that would be expected during normal production. Media-fill validations should be repeated with sufficient frequency to ensure the ongoing capability of performing properly each aseptic processing operation used in the authorized facility. The frequency and results of media-fill runs should be documented.

The culture medium selected should be capable of supporting the growth of a broad spectrum of microorganisms likely to be production-associated contaminants in the authorized facility. Commercially available media can be obtained that, when reconstituted as directed by the manufacturer, are certified to have growth-promoting properties. Soybean–Casein Digest Medium is acceptable (see *Sterility Tests* ⟨71⟩). Incubation of medium-filled

[2] FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987, pp. 20-27; PDA Technical Monograph No. 2, Validation of Aseptic Filling for Solution Drug Products, 1980.

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units should take at least 14 days and may be at room temperature for 14 days or may be at room temperature for the first 7 days, with the final 1 to 7 days at 30° to 35°. Alternate suitable incubation schedules may be used as determined by the pharmacy to ensure enough growth of any potential contaminating microorganisms to be visually detectable. Microorganisms in all medium-filled units showing visible evidence of microbial growth should be promptly identified, and if this growth exceeds the action limits, an immediate investigation should be made with prompt correction of any identifiable causes of the failure. Review of environmental monitoring data obtained during the media fill should be included in the investigation, aswell as a review of the cleaning, sanitizing, disinfection, production procedures, aseptic technique, personnel practices, and other factors as appropriate. Revalidation should occur after all media-fill failures (see *Table 1*).

Table 1. Media-Fill Validation of Aseptic Processing

Validation Purpose	Minimum Validation Requirements: Low- and Medium-Risk CSPs	Minimum Validation Requirements: High Risk CSPs*
General	Personnel validation	Process validation
Initial	3 consecutive media-fill runs without contamination	3 consecutive media-fill runs without contamination
Revalidation	1 media-fill run quarterly without contamination	annual media-fill run without contamination
Failure Revalidation	3 consecutive media-fill runs without contamination	3 consecutive media-fill runs without contamination

* NOTE—Personnel should have first passed low- and medium-risk validation. ●4

Delete the following:

•LOW-RISK OPERATIONS

A quality assurance program should include a system that incorporates validation and monitoring processes that ensure a compounded sterile preparation meets predetermined, specific criteria of quality. The primary objective of the validation of aseptic processing involving low-risk operations is to ensure that personnel are capable of using effective aseptic technique to compound an SP successfully under the most rigorous conditions encountered during normal work assignments. The validation program should include a system of proofs that show that processes and operators are appropriate for achieving predefined product-quality conditions and personnel have skills to perform those compounding activities reproducibly and repeatedly. The validation of the process includes media fills consisting of a planned repetitive sequence of compounded or repackaged units. The number of manipulations of each unit and the number of units in each media fill should reflect the most complex and prolonged aseptic manipulations likely to be encountered by an operator as a normal workload requirement. The number of units per media-fill run should be enough to ensure that the operator is capable of replicating acceptable aseptic procedures. A sampling plan and validation requirements are defined in written procedures. Media transfers could be used to represent procedures such as syringe transfers, use of automated compounding devices, multiple additive procedures, and various aseptic assemblies and connections. An example of a validation procedure for low-risk operations is as follows.

Scenario—A pharmacy prepares antibiotics, hydration solutions, and parenteral nutrition solutions. Low-risk CSP processing would include the reconstitution and preparation of antibiotics for administration of single units at set intervals. Many of these products are prepared in batches and stored in anticipation of future use. Operators should be trained and their techniques validated using a sterile culture medium to simulate the syringe transfer of diluent to reconstitute lyophilized antibiotics, the transfer of that product to an empty sterile bag, bottle, or syringe; and any other manipulations that may be routine in the admixture processes.

Example of a Validation Procedure—Six 25-mL aliquots of sterile Soy–Casein Digest Medium are aseptically transferred to separate, empty 30-mL sterile vials. Ten milliliters of sterile Soy–Casein Digest Medium is removed from one of the vials and added to a vial of sterile, lyophilized Polyethylene Glycol. Four 2.5-mL aliquots of the resulting solution are added to 30-mL vials already containing 25-mL sterile Soy–Casein Digest Medium, and the vials are labeled. The six 30-mL vials are incubated at room temperature for a total of 14 days, with frequent checks for growth.

Media fills should be representative of peak periods of fatigue, stress, and pacing demands. For example, media fills could be scheduled immediately after normal production activity has ended. Media fills should not be performed during normal production.

Operators should pass an initial validation, performing three media fills with no contamination, before they are allowed to compound CSPs for patients. Subsequently, each operator should perform at least one media fill involving low-risk operations quarterly. If one contaminated unit results from a media fill, the operator should be retrained and then perform three consecutive media fills with no evidence of contamination before resuming preparation of CSPs for patients. Operators should also be revalidated if the nature of their aseptic compounding assignments changes to the extent that their previous media fills are not representative of their revised assignments.

Quality assurance programs for low-risk CSPs also include a system that employs routine methods to ensure that the finished products are reviewed for compounding accuracy and potential hazards, such as particulate matter, microorganisms, pyrogens, allergens, and cross-contamination from other drugs that may have been introduced into the compounding environment. Final products are inspected for particulate matter and leakage before release. A predetermined percentage of compounded products could be sequestered for routine sterility and pyrogen testing. Allergens and cross-contamination are best controlled through the strict adherence to proper procedures, which limit or eliminate the introduction of the allergens, and to frequent cleaning to reduce the potential of lingering drug residues in the work area. Personnel are trained in the proper methods of eliminating allergens and cleaning and disinfecting the workstation. That training is reviewed periodically.●4

Delete the following:

•HIGH-RISK OPERATIONS

In the case of high-risk operations, the focus of validation is on the process as well as personnel capability. Thus, the primary objective of the validation of aseptic processing for high-risk CSP operations is to ensure that the aseptic process is capable of being carried out consistently under control by any qualified operator, before the process is utilized for production of units intended for administration to patients. Accordingly, each type of high-risk operation is validated independently, rather than having operators perform representative sets of aseptic activities, as is the case with low-risk and medium-risk aseptic operations.

Personnel assigned to high-risk aseptic operations should be validated for low-risk and medium-risk operations as described above. In addition, this personnel should participate, at least annually, in the validation of each high-risk aseptic operation to which they are assigned.

For example, for high-risk operations involving nonsterile components, the media-fill run should simulate as closely as possible the most intensive conditions likely to be encountered during the normal production activities. The number of units in a media-fill run should be no less than the largest number of units encountered during production involving the process being validated. However, the fill volume of media-fill units need not equal the fill volume of finished product units.

A media-fill run should be performed at least annually for each unique high-risk batch processing procedure and configuration. A media-fill failure for most operations (less than 1000 units) is one or more contaminated units after incubation. For batches equal to or greater than 1000 units, a media-fill failure is greater than one contaminated unit. When a media-fill failure occurs, three consecutive successful media fills should occur before the process failing the media fill may be used for the preparation of a CSP for patients. An example of a validation procedure for a high-risk operation is as follows:

Scenario—A pharmacy prepares individual cassettes of morphine for epidural use from morphine powder. The nonsterile powder is weighed, and then placed in the barrel of a 60-mL syringe. After replacing the syringe plunger, sterile 5% dextrose solution is drawn into the syringe to make a total volume of 50 mL. After shaking to dissolve the powder, a 0.22-µm disk filter is placed on the syringe, and the solution is pushed through the filter into a drug reservoir cassette for an ambulatory infusion pump. Typically, the pharmacy prepares a week's supply of two to three cassettes at one time.

Example of a Validation Procedure—A small quantity of an inert powder (for example, lactose or sugar) is placed in the barrel of a 60-mL syringe. After replacing the syringe plunger, sterile 5% dextrose solution is withdrawn into the syringe to make a total volume of 50 mL. A sterile 0.22-µm filter is connected to the syringe tip. After shaking to dissolve the powder, the solution is pushed through the filter: the first 5 mL are aseptically introduced into a test tube containing 10 mL of sterile Soybean–Casein Digest Medium; the next 40 mL are discarded in a sterile container; and the last 5 mL are aseptically introduced into another tube containing 10 mL of sterile Soybean–Casein Digest Medium. At least three syringes should be evaluated in this manner. The inoculated tubes of Medium should be incubated at 20° to 25° for 14 days, with frequent visual observations made for growth of microorganisms.●4

Add the following:

•PERSONNEL TRAINING AND EVALUATION IN ASEPTIC MANIPULATION SKILLS

Personnel who prepare CSPs must be provided with appropriate training from expert personnel, audio–video instructional sources, and professional publications in the theoretical principles and practical skills of aseptic manipulations before they begin to prepare CSPs. Compounding personnel shall perform didactic review, and pass written and media-fill testing of aseptic manipulative skills initially; at least annually thereafter for low- and medium-risk level compounding; and semi-anually for high-risk level compounding. Compounding personnel who fail written tests, or whose media-fill test vials result in gross microbial colonization, must be immediately re-instructed and re-evaluated by expert compounding personnel to assure correction of all aseptic practice deficiencies.

Media-Fill Challenge Testing—The skill of personnel to aseptically prepare CSPs may be evaluated using sterile fluid bacterial culture media-fill validation,[1] (i.e., sterile bacterial culture medium transfer via a sterile syringe and needle). Media-fill testing is used to assess the quality of the aseptic skill of compounding personnel. Media-fill tests represent the most challenging or stressful conditions actually encountered by the personnel being evaluated when they prepare particular risk level CSPs and when sterilizing high-risk level CSPs.

Commercially available sterile fluid culture media, such as Soybean–Casein Digest Medium (see *Sterility Tests* ⟨71⟩), shall be able to promote exponential colonization of bacteria that are most likely to be transmitted to CSPs from the compounding personnel and environment. Media-filled vials are incubated at 25° to 35° for 14 days. Failure is indicated by visible turbidity in the medium on or before 14 days.

Example of a Media-Fill Test Procedure—Perform the test as directed in the section *Quality Assurance of Low-Risk Level CSPs*.●4

Change to read:

ENVIRONMENTAL QUALITY AND CONTROL

Achieving and maintaining sterility and overall freedom from contamination of a pharmaceutical product is dependent upon the quality status of the components incorporated, the process utilized, personnel performance, and the environmental conditions under which the process is performed. The standards required for the environmental conditions depend upon the amount of exposure of the CSP to the immediate environment anticipated during processing. The quality and control of environmental conditions for •each risk level of operation●4 is explained in this section. In addition, operations using nonsterile components require the use of a method of preparation designed to produce a sterile product.

Critical Site Exposure

The degree of exposure of the product during processing will be affected by the length of time of exposure, the size of the critical site exposed, and the nature of the critical site.

A critical site is any opening providing a direct pathway between a sterile product and the environment or any surface coming in direct contact with the product and the environment. The risk of such a site picking up contamination from the environment increases with time of exposure. Therefore, the processing plan and the intent of the operator should give due consideration to organization, efficiency, and speed in order to keep such exposure time to a minimum. For example, an ampul should not be opened unnecessarily in advance of use.

The size of the critical site affects the risk of contamination entering the product: the greater the exposed area, the greater the risk. An open vial or bottle exposes to contamination a critical site of much larger area than the tip of a 26-gauge needle. Therefore, the risk of contamination when entering an open vial or bottle is much greater than during the momentary exposure of a needle tip.

The nature of a critical site also affects the risk of contamination. The relatively rough, permeable surface of •an elastomeric●4 closure retains microorganisms and other contaminants, after swabbing with an alcohol pad, more readily than does the smooth glass surface of the neck of an ampul. Therefore, the surface dis-

[1] FDA Guideline on Sterile Drug Products Produced by Aseptic Processing, June 1987, pp. 20-27; PDA Technical Monograph No. 2, Validation of Aseptic Filling for Solution Drug Products, 1980.

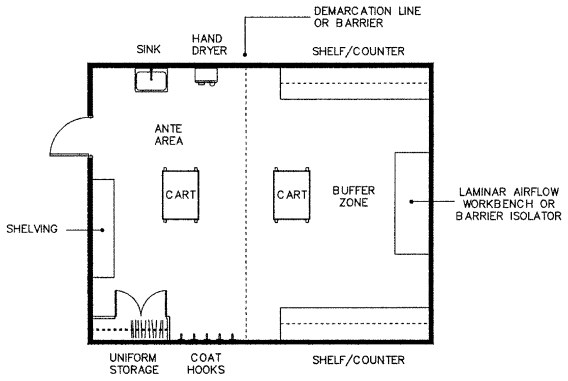
infection can be expected to be more effective for an ampul.• Once the ampul is open, the critical site of exposure is greatly increased, creating a pathway with the potential for introduction of glass, fiber, and dust into the fluid contained in the ampul.•[4]

The prevention or elimination of airborne particles must be given high priority. •[4] Airborne contaminants are much more likely to reach critical sites than contaminants that are adhering to the floor or other surfaces below the work level. Further, particles that are relatively large or of high density settle from the airspace more quickly and thus can be removed from the vicinity of critical sites.

•Clean Rooms and Barrier Isolators

In general, sterile product preparation facilities utilize laminar airflow workbenches (LAFWs) to provide an adequate critical site environment. A discussion of the necessary facilities and proper procedures for preparing sterile products using LAFWs in clean rooms is presented below. The use of alternative systems in clean rooms that have been verified to achieve the same or better level of environmental quality as that achieved by properly operated LAFWs may also be utilized. An emerging alternative technology utilizes barrier isolator systems to minimize the extent of personnel contact and interaction, to separate the external environment from the critical site, and to provide an ISO Class 5 environment (see *Table 1*) for preparing CSPs. A well-designed positive pressure barrier isolator, supported by adequate procedures for its maintenance, monitoring, and control, may offer an acceptable alternative to the use of conventional LAFWs in clean rooms for aseptic processing. An example of the arrangement of a clean-room floor plan for low- and medium-risk level CSPs is illustrated in the first drawing in *Figure 1*. The second drawing in *Figure 1* depicts an appropriate multicompartment clean-room floor plan for high-risk level CSPs.

EXAMPLE OF CLEAN ROOM FLOOR PLAN SUITABLE FOR LOW AND MEDIUM RISK-LEVEL CSPs



EXAMPLE OF CLEAN ROOM FLOOR PLAN SUITABLE FOR HIGH RISK-LEVEL CSPs

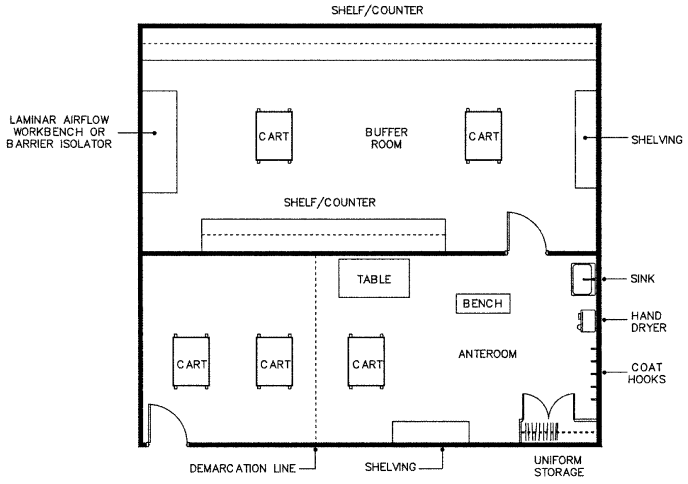


Fig. 1

Environmental Controls

Engineering controls reduce the potential for airborne contamination in workspaces by limiting the amount and size of contaminants in the CSP processing environment. Primary engineering controls are used and generally include horizontal flow clean benches, vertical flow clean benches, biological safety cabinets, and barrier isolators. Primary environmental control must provide at least ISO Class 5 quality of air (see *Table 1*) to which sterile ingredients and components of CSPs are directly exposed. Secondary engineering controls generally provide a buffer zone or buffer room as a core for the location of the workbenches or isolators.

Table 1. International Organization of Standardization (ISO) Classification of Particulate Matter in Room Air [Limits are in particles 0.5 μm and larger per cubic meter (current ISO) and cubic feet (former Federal Standard No. 209E, FS209E).]*

Class Name		Particle Size	
ISO Class	U.S. FS 209E	ISO, m^3	FS 209E, $ft.^3$
3	Class 1	35.2	1
4	Class 10	352	10
5	Class 100	3520	100

Class Name		Particle Size	
ISO Class	U.S. FS 209E	ISO, m^3	FS 209E, $ft.^3$
6	Class 1000	35,200	1000
7	Class 10,000	352,000	10,000
8	Class 100,000	3,520,000	100,000

* Adapted from the Federal Standard No. 209E, General Services Administration, Washington, DC, 20407 (September 11, 1992) and ISO [4644-1:1999 Clean rooms and associated controlled environments—Part 1: Classification of air cleanliness. For example, 3520 particles of 0.5 µm per m_3 or larger (ISO Class 5) is equivalent to 100 particles per ft_3 (Class 100) (1 m_3 = 34.314 $ft._3$).

Airflow through high-efficiency particulate air (HEPA) filters is unidirectional or columnar, and because of the pore size of the filter the "first air" at the face of the filter is, for the purposes of aseptic compounding, free from airborne particulate contamination. Barrier isolators provide a suitable environment by restricting any ambient air from the work chamber. These systems are not as sensitive to external environments as the HEPA-filtered unidirectional airflow units.

Several aspects of barrier isolation and filtered unidirectional airflow in work environment must be understood and practiced in the compounding process. Policies and procedures for maintaining and working in the prescribed conditions for aseptic processing must be prepared, updated, maintained, and implemented and are determined by the scope and risk levels of the activities undertaken in the SP compounding operation.

In general, the CSP work environment is designed to have the cleanest work surfaces (horizontal or vertical clean benches, biological safety cabinets, or isolators) located in a buffer area, which is preceded by an anteroom that provides a clean area for donning personnel barriers, such as hair covers, gloves, gowns, or full clean-room attire. The class limit of the buffer or core room has to be demonstrably better than that of ambient air to reduce the risk of contaminants being blown, dragged, or otherwise introduced into the filtered unidirectional airflow environment. For example, strong air currents from opened doors, personnel traffic, or air streams from the heating, ventilating, and air-conditioning systems can easily disrupt the unidirectional, columnar airflow in the open-faced workbenches. The operators may also introduce disruptions in flow by their own movements and by the placement of objects onto the work surface.

Buffer or clean-room areas in which LAFWs are located are to provide at least ISO Class 8 air quality (see Table 1). Measuring, weighing, mixing, and other manipulations of nonsterile in-process CSPs are also performed in air quality of at least ISO Class 8 (see *Table 1*). Appropriate air conditioning and humidity controls must be in place for the buffer area.●4

Tasks carried out within the buffer area should be limited to those for which a controlled environment is necessary. Only the furniture, equipment, supplies, and other goods required for the tasks to be performed may be brought into this room, and they should be nonpermeable, nonshedding, and resistant to disinfectants. Whenever such items are brought into the room, they should first be cleaned and sanitized. Whenever possible, equipment and other items used in the buffer area should not be taken from the room except for calibration, servicing, or other activity associated with the proper maintenance of the item.

The surfaces of ceilings, walls, floors, fixtures, shelving, counters, and cabinets in the buffer area should be smooth, impervious, free from cracks and crevices, and nonshedding, thereby promoting cleanability and minimizing spaces in which microorganisms and other contaminants may accumulate. The surfaces should be resistant to damage by sanitizing agents. Junctures of ceilings to walls should be coved or caulked to avoid cracks and crevices where dirt can accumulate. If ceilings consist of inlaid panels, the panels should be impregnated with a polymer to render them impervious and hydrophobic, and they should be caulked around each perimeter to seal them to the support frame. Walls may be of panels locked together and sealed or of epoxy-coated gypsum board. Preferably, floors are overlaid with wide sheet vinyl flooring with heat-welded seams and coving to the sidewall. Dust-collecting overhangs, such as ceiling utility pipes, or ledges, such as windowsills, should be avoided. The exterior lens surface of ceiling lighting fixtures should be smooth, mounted flush, and sealed. Any other penetrations through the ceiling or walls should be sealed.

The buffer area should contain no sinks or floor drains. Work surfaces should be constructed of smooth, impervious materials, such as stainless steel or molded plastic, so that they are readily cleanable and sanitizable. Carts should be of stainless steel wire or sheet metal construction with good quality, cleanable casters to promote mobility. Storage shelving, counters, and cabinets should be smooth, impervious, free from cracks and crevices, nonshedding, cleanable, and sanitizable. Their number, design, and manner of installation should promote effective cleaning and sanitizing.

•CSP Environment

The contamination reduction conditions and procedures in this section include LAFWs being located within buffer or clean-room areas that maintain at least an ISO Class 8 (see *Table 1*). It is preferred, but not necessary, to locate barrier isolators within such a buffer air quality area. The frequency and amount of personnel access to buffer air quality areas is restricted to minimize contaminants, while allowing delivery of essential materials for CSPs. Food, drinks, and materials exposed in patient care and treatment areas must never be introduced into areas where components and ingredients for CSPs are present.

In an area near, but physically isolated from the buffer room area—the anteroom area—supplies, such as needles, syringes, ampuls, bags, vials of parenteral fluids, and packages of transfer tubing sets for large-volume fluids are uncartoned and disinfected.

Hand sanitizing and gowning activities also occur in the anteroom area adjacent to the buffer area. Faucet handles are designed to be hands-free. Before processing CSPs, hands are resanitized after donning all appropriate garb, except for gloves. A demarcation line or barrier identifies the separation of the buffer area from the anteroom area. Compounding personnel must be capable of accessing the buffer area without use of their hands. Anteroom areas adjacent to buffer areas are intended to minimize the introduction of contaminants into buffer areas.●4

Cleaning and Sanitizing the Workspaces

The cleaning, sanitizing, and organizing of the •direct and contiguous compounding areas (DCCA) is●4 the responsibility of trained operators (pharmacists and technicians) following written procedures and •is●4 performed at the beginning of each shift. •Before compounding is performed, all items are●4 removed from the •DCCA and all surfaces are cleaned of loose material and residue

from spills, followed by an application of a residue-free sanitizing agent[2] that is left on for a time sufficient to exert its antimicrobial effect.

Work surfaces near the DCCA in the buffer or clean area are cleaned in a similar manner, including counter tops and supply carts. Storage shelving is emptied of all supplies and then cleaned and sanitized at least weekly, using approved agents.

Floors in the buffer or clean area are cleaned by mopping once daily when no aseptic operations are in progress. Mopping may be performed by trained and supervised custodial personnel using approved agents described in the written procedures. Only approved cleaning and sanitizing agents are used with careful consideration of compatibilities, effectiveness, and inappropriate or toxic residues. Their schedules of use and methods of application are in accord with written procedures. All cleaning tools, such as wipers, sponges, and mops, are nonshedding and dedicated to use in the buffer or clean area. Floor mops may be used in both the buffer or clean area and anteroom area, but only in that order. Most wipers are discarded after one use. If cleaning tools are reused, their cleanliness is maintained by thorough rinsing and sanitization after use and by storing in a clean environment between uses. Trash is collected in suitable plastic bags and removed with minimal agitation.

In the anteroom area, supplies and equipment removed from shipping cartons are wiped with a sanitizing agent, such as sterile 70% isopropyl alcohol (IPA)[3] , which is checked periodically for contamination. Alternatively, if supplies are planned to be received in sealed pouches, the pouches can be removed as the supplies are introduced into the buffer or clean area without the need to sanitize the individual supply items. No shipping or other external cartons may be taken into the buffer or clean area. Cleaning and sanitizing of the anteroom area is performed at least weekly by trained and supervised custodial personnel, in accordance with written procedures. However, floors are cleaned and sanitized daily, always proceeding from the buffer or clean area to the anteroom area. Storage shelving is emptied of all supplies and cleaned and sanitized at planned intervals, preferably monthly.

These cleaning and sanitizing procedures apply to both low-risk and high-risk operations.

Personnel Cleansing and Gowning

Personnel are critical keys to the maintenance of asepsis when carrying out their assigned responsibilities. They must be thoroughly trained in aseptic techniques and be highly motivated to maintain these standards each time they prepare a sterile product.

Prior to entering the buffer or clean area, operators should remove outer lab jackets or the like, makeup, and jewelry and should thoroughly scrub hands and arms to the elbow. After drying hands and arms they should properly don clean, nonshedding uniform components, including hair covers, shoe covers, knee-length coats or coveralls, and appropriate protective gloves, in that order. The coats should fit snugly at the wrists and be zipped or snapped closed in the front. Shoe covers should be donned so that feet then touch the floor only on the clean side of the bench or other demarcation. Face masks should be donned just before beginning activities in the DCCA to minimize airborne contaminants from coughing, sneezing, and talking. When preparing CSPs in a vertical flow LAFW with a transparent shield between the face of the operator and sterile components, or when using an isolator, wearing a face mask is optional, but head and facial hair must be covered.

Appropriate powder-free protective gloves are sterile or, if nonsterile, are sanitized with an appropriate antimicrobial cleaner such as 70% alcohol before use. Protective gloves are put on as the last uniform component. When nonsterile gloves, chosen for their chemically protective composition, are used, they are disinfected with sterile 70% isopropyl alcohol or an antimicrobial agent that is allowed to evaporate before beginning compounding procedures. Sterile and sanitized gloves do not remain sterile and clean during compounding activities because they come in contact with nonsterile surfaces and air. Therefore, compounding personnel must be trained to avoid touching sterile surfaces of packages, transfer devices, and components within ISO Class 5 or superior environments (see *Table 1*). During protracted compounding activities, personnel should intermittently resanitize their gloves with sterile 70% isopropyl alcohol.

Proper scrubbing and gowning immediately prior to entry into the buffer or clean area is required of all personnel, without exception. Should the operator find it necessary to leave the room, the coat may be carefully removed at the entrance and hung inside out for redonning upon re-entry, but only during the same shift. However, hair covers, masks, shoe covers, and gloves should be discarded and new ones donned prior to re-entry.

For high-risk operations, it is especially critical to minimize the risk of contamination on lab coats, coveralls, and other garb to be worn in the buffer or clean area. Preferably, fresh clean garb should be donned upon each entry into the buffer or clean area to avoid liberating contaminants from previously worn garb. Alternatively, garb that has been worn may be removed with the intention of regarbing for re-entry into the buffer or clean area and stored during the interim under proper control and protection in the anteroom area. Garb worn or taken outside the confines of the anteroom area cannot be worn in the buffer or clean area.

Dispersion of particles from body surfaces, such as from skin rashes, sunburn, or cosmetics, increases the risk of contamination of critical sites and must be appropriately controlled or minimized. If severe, the operator must be excluded from the buffer or clean area until the condition is remedied, especially for high-risk operations.

Suggested Standard Operating Procedures

The pharmacy should have written, properly approved standard operating procedures (SOPs) designed to ensure the quality of the environment in which a CSP is prepared. The following procedures are recommended:

(1) Access to the buffer or clean area is restricted to qualified personnel with specific responsibilities or assigned tasks in the area.

(2) All cartoned supplies are decontaminated in the anteroom area by removing them from shipping cartons and wiping or spraying with a disinfecting agent, such as sterile IPA, while being transferred to a clean, sanitized cart or other conveyance for introduction into the buffer or clean area. Individual pouched supplies need not be wiped because the pouches can be removed as these supplies are introduced into the buffer or clean area.

(3) Supplies required frequently or otherwise needed close at hand but not necessarily needed for the scheduled operations of the shift are decontaminated and stored on the shelving in the anteroom area.

(4) Carts used to bring supplies from the storeroom cannot be rolled beyond the demarcation line in the anteroom area, and carts used in the buffer or clean area cannot be rolled outward beyond the demarcation line unless cleaned and sanitized before returning.

(5) Generally, supplies required for the scheduled operations of the shift are prepared and brought into the buffer or clean area, preferably on one or more movable carts. Supplies that

[2] Approved by the pharmacist in charge.

[3] NOTE—70% isopropyl alcohol (IPA) may harbor resistant microbial spores. Therefore, IPA used in aseptic areas should always be filtered through a 0.2-µm hydrophobic filter to render it sterile.

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are required for back-up or general support of operations may be stored on the designated shelving in the •buffer or clean area,•4 but •avoid•4 excessive accumulation of supplies. •4

(6) Objects that shed particles •cannot•4 be brought into the •buffer or clean area,•4 including pencils, cardboard cartons, paper towels, and cotton items. •Only nonshedding paper-related products (boxes, work records, and so forth) can be brought into the buffer or clean area.•4

(7) Traffic flow in and out of the •buffer or clean area must be•4 minimized.

(8) Personnel preparing to enter the •buffer or clean area must•4 remove all jewelry from hands and arms.

(9) Personnel entering the •buffer or clean area must•4 first scrub hands and arms with soap, including using a scrub brush on the fingers and nails. An air dryer or disposable nonshedding towels •are•4 used to dry hands and arms after washing.

(10) Personnel entering the •buffer or clean area,•4 after scrubbing, should don attire as described under •*Personnel Cleansing and Gowning*.•4

(11) No chewing gum, candy, or food items may be brought into the •buffer or clean area or anteroom area.•4

(12) •At the beginning of each compounding activity session, and after liquids are spilled, the surfaces of the direct compounding environment are first cleaned with *Purified Water* to remove water soluble residues. Immediately thereafter, the same surfaces are sanitized with sterile 70% isopropyl alcohol, or other effective antimicrobial agents, using a nonlinting wipe.•4

(13) •When LAFWs or barrier isolators are used as the ISO Class 5 air quality environment (see Table 1), their blowers must be operated continuously during compounding activity, including during interruptions of less than 8 hours. When the blower is turned off and before other personnel enter to perform compounding activities, only one person can enter the contiguous buffer area for the purposes of turning on the blower (for at least 30 minutes) and of sanitizing the work surfaces.•4

(14) Traffic in the area of the •DCCA is•4 minimized and controlled. The •DCCA is•4 shielded from all less clean air currents that are of higher velocity than the clean laminar airflow.

(15) Supplies to be utilized in the •DCCA•4 for the planned procedures •are•4 accumulated and then decontaminated by wiping •or spraying•4 the outer surface with IPA or removing the outer wrap at the edge of the •DCCA•4 as the item is introduced into the aseptic work area.

(16) After proper introduction into the •DCCA•4 of supply items required for and limited to the assigned operations, they •are•4 so arranged that a clear, uninterrupted path of HEPA-filtered air will bathe all critical sites at all times during the planned procedures. That is, no objects may be placed behind an exposed critical site in a horizontal position or above in the vertical laminar flow workbench.

(17) All supply items •are arranged in the DCCA so as•4 to reduce clutter and to provide maximum efficiency and order for the flow of work.

(18) All procedures •are•4 performed in a manner designed to minimize the risk of touch contamination. Gloves •are•4 sanitized with adequate frequency •with an approved disinfectant.•4

(19) All rubber stoppers of vials and bottles and the neck of ampuls •are•4 sanitized with IPA prior to the introduction of a needle or spike for the removal of product.

(20) After the preparation of every admixture, the contents of the container •are•4 thoroughly mixed and then inspected for the presence of particulate matter, evidence of incompatibility, or other defects.

(21) After procedures are completed, used syringes, bottles, vials, and other supplies •are•4 removed, but with a minimum of exit and re-entry into the •DCCA•4 to minimize the risk of introducing contamination into the aseptic workspace.

•Environmental Monitoring

In addition to the evaluation and verification of personnel aseptic techniques and of the adequacy of compounding processes and procedures (see *Personnel Training and Evaluation in the Aseptic Manipulation Skills* section), assessment and verification of the adequacy of the sterile compounding environment is essential, especially for preparing high-risk preparations. Evaluation of environmental quality is performed by measuring both the total number of particles and the number of viable microorganisms in the controlled air environments of the compounding area.

Certification that each LAFW and barrier isolator is functioning properly and meets the air quality requirement of ISO Class 5 (refer to *Clean Rooms and Barrier Isolators* and Table 1 in the *Environmental Quality and Control* section) is performed by a qualified operator(s) using current, state-of-the-art electronic air sampling at least every six months and whenever the LAFW or barrier isolator is relocated. Similarly, the air quality of the buffer or clean area and anteroom area is evaluated by a qualified operator(s) for conformance to ISO Class 7 and ISO Class 8 requirements, as appropriate, at least every six months and when renovations occur. These records are maintained and reviewed by the supervising pharmacist or other designated employee.

Evaluation of airborne microorganisms in the controlled air environments (LAFW, barrier isolators, buffer or clean area, and anteroom area) is performed by properly trained individuals using suitable electric air samplers or by exposing sterile nutrient agar plates for a suitable time frame. For either approach, the air sampling is performed at locations judged by compounding personnel to be the most prone to contamination during compounding activities: this includes zones of air backwash turbulence within LAFWs and other areas where air backwash turbulence may enter the compounding area. Such evaluations are performed as a regular and ongoing process at least monthly for sterile compounding areas used for low- and medium-risk preparations and at least weekly for areas used for high-risk preparations.

For electric air samplers that actively collect volumes of air for evaluation, the instructions for verification and use of these devices must be followed. When using the passive exposure of sterile nutrient agar settling plates, the covers are removed and the media is exposed for a period usually lasting 1 hour or longer to collect viable microorganisms as they fall from the environment. At the end of the designated exposure period, the plates are recovered and incubated at a temperature and for a time period conducive to multiplication of microorganisms on the nutrient agar—usually at 30° to 35° for a minimum of 48 hours. The number of discrete colonies of microorganisms are then counted and reported as colony forming units (cfu). This provides a measurement of the level of microbial contamination in the air within the tested environment.

The greatest value of viable microorganism monitored in the air of the compounding environment is realized when normal baseline cfu counts are determined over a period of time. Determining the baseline cfu counts permits identification of a trend toward increasing microbial cfu counts. A sufficiently increasing trend in cfu counts over time must prompt a re-evaluation of the adequacy of cleaning procedures, operational procedures, and air filtration efficiency within the sterile compounding location. Action may be warranted when an increasing trend to 50% above the baseline for areas used for high- and medium- risk preparations or to 100% above baseline for areas used for low-risk preparations is found.

A written plan and schedule for the environmental monitoring procedures for airborne microorganisms must be established and followed. The plan must be adequate to evaluate the various controlled air environment areas (LAFW, barrier isolator, buffer or clean area, and anteroom area) of the sterile compounding facility. All compounding personnel are trained in and educated about the importance of this environmental monitoring process. For sterile compounding areas used for low- and medium-risk preparations,

a minimum of monthly evaluation is appropriate. For sterile compounding areas used for high-risk preparations, at least weekly evaluation is appropriate.•4

Change to read:

PROCESSING

•A written description of specific training and performance evaluation program for individuals involved in the use of aseptic techniques for the preparation of sterile products must be developed for each site. This program equips the personnel with the appropriate knowledge and trains them in the required skills necessary to perform the assigned tasks. Each person assigned to the aseptic area in the preparation of sterile products must successfully complete specialized training in aseptic techniques and aseptic area practices prior to preparing CSPs (see the *Personnel Training and Evaluation in Aseptic Manipulation Skills* section).

Aseptic Technique

Critical operations are carried out by appropriately trained and qualified personnel in a DCCA using proper aseptic techniques described in a written procedure (see *Suggested Standard Operating Procedures*). Aseptic technique is equally applicable to the preparation of sterile sensitizing and chemotoxic agents. However, it is essential to recognize that additional precautions must be utilized to protect the personnel and the compounding environment from the potential adverse effects of these chemotoxic products. The minimum requirements for this process include the following: working and verified vertical laminar airflow work bench, barrier isolator, or other environmental containment and control device with biohazard control capabilities; the protective capabilities of gowns, masks, bouffants, and gloves; sprayback and spill control techniques and equipment; the use specialized compounding devices and equipment; and proper disposal.•4

Components

•Compounding personnel ascertain that ingredients for CSPs are of the correct identity and appropriate quality using the following information: vendors' labels, labeling, certificates of analysis, direct chemical analysis, and knowledge of compounding facility storage conditions.•4

STERILE •INGREDIENTS AND•4 COMPONENTS

Commercially available sterile drug products, sterile ready-to-use containers and devices are examples of sterile components. A written procedure for unit-by-unit physical inspection preparatory to use •is•4 followed to ensure that these components are sterile, free from defects, and otherwise suitable for their intended use.

NONSTERILE •INGREDIENTS AND•4 COMPONENTS

•If any nonsterile components, including containers, devices, and ingredients are used to make a CSP, such CSPs must be compounded at a high-risk level. Nonsterile active ingredients and added substances, or excipients, for CSPs should preferably be official *USP* or *NF* articles. When nonofficial ingredients are used, they must be accompanied by certificates of analysis from their suppliers to aid compounding personnel in judging the identity, quality, and purity in relation to the intended use in a particular CSP. Physical inspection of a package of ingredients is necessary in order to detect breaks in the container, looseness in the cap or closure, and deviation from the expected appearance, aroma, and texture of the contents.

Bulk, or unformulated, drug substances and added substances, or excipients, must be stored in tightly closed containers under temperature, humidity, and lighting conditions that are either indicated in official monographs or approved by suppliers; also the date of receipt in the compounding facility must be clearly and indelibly marked on each package of ingredient. After receipt by the compounding facility, packages of ingredients that lack a supplier's expiration date cannot be used after one year, unless either appropriate inspection or testing indicates that the ingredient has retained its purity and quality for use in CSPs.

Careful consideration and evaluation of nonsterile ingredient sources is especially warranted when the CSP will be administered into the vascular, central nervous system, and eyes.

Upon receipt of each lot of the bulk drug substance or excipient used for CSPs, the individual compounding the preparation performs a visual inspection of the lot for evidence of deterioration, other types of unacceptable quality, and wrong identification. The bulkdrug substance or excipient visual inspection is performed on a routine basis as described in the written protocol.•4

Equipment

•It is necessary that equipment, apparatus, and devices used to compound a CSP are consistently capable of operating properly and within acceptable tolerance limits. Written procedures outlining required equipment calibration, annual maintenance, monitoring for proper function, controlled procedures for use of the equipment and specified time frames for these activities are established and followed. Routine maintenance and time intervals are also outlined in these written procedures. Results from the equipment calibration, annual maintenance reports, and routine maintenance are kept on file for the lifetime of the equipment. Personnel is prepared through an appropriate combination of specific training and experience to operate or manipulate any piece of equipment, apparatus, or device they may use when preparing CSPs. Training includes gaining the ability to determine whether any item of equipment is operating properly or is malfunctioning.•4

Add the following:

•VERIFICATION OF AUTOMATED COMPOUNDING DEVICES FOR PARENTERAL NUTRITION COMPOUNDING

Automated compounding devices (ACDs) for the preparation of parenteral nutrition admixtures are widely used by pharmacists in hospitals and other health care settings. They are designed to streamline the labor-intensive processes involved in the compounding of these multiple-component formulations by automatically delivering the individual nutritional components in a predetermined sequence under computerized control. Parenteral nutrition admixtures often contain 20 or more individual additives representing as many as 50 or more individual components (e.g., 15 to 20 crystalline amino acids, dextrose monohydrate, and lipids; 10 to 12 electrolyte salts; 5 to 7 trace minerals; and 12 vitamins). Thus, the ACDs can improve the accuracy and precision of the

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compounding process compared to the traditional, manual compounding methods. Pharmacists should consult the general information chapter *Validation of Compendial Methods* ⟨1225⟩ for verification parameters to be considered when evaluating an ACD.

Accuracy

The accuracy of an ACD can be determined in various ways to ensure that the correct quantities of nutrients, electrolytes, or other nutritional components are delivered to the final infusion container. Initially, the ACD is tested for its volume and weight accuracy. For volume accuracy, a suitable volume of *Sterile Water for Injection*, which represents a typical additive volume (e.g., 40 mL for small-volume range of 1 to 100 mL; or 300 mL for large-volume range of 100 to 1000 mL), is programmed into the ACD and delivered to the appropriate volumetric container. The pharmacist then consults *Volumetric Apparatus* ⟨31⟩ for appropriate parameters to assess the volumetric performance of the ACD. For gravimetric accuracy, the balance used in conjunction with the ACD is tested using various weight sizes that represent the amounts typically used to deliver the various additives. The pharmacist consults *Weights and Balances* ⟨41⟩ for acceptable tolerances of the weights used. In addition, the same volume of *Sterile Water for Injection* used to assess volumetric accuracy is then weighed on the balance used in conjunction with the ACD. For example, if 40 mL of water was used in the volumetric assessment, its corresponding weight should be about 40 g (assuming the relative density of water is 1.0). In addition, during the use of the ACD, certain additives, such as potassium chloride (corrected for density differences) can also be tested in the same manner as an in-process test.

Finally, additional tests of accuracy may be employed that determine the content of certain ingredients in the final volume of the parenteral nutrition admixture. Generally, pharmacy departments do not have the capability to routinely perform chemical analyses such as analyses of dextrose or electrolyte concentrations. Consequently, hospital or institutional laboratories may be called upon to perform these quality assurance tests. However, the methods in such laboratories are often designed for biological, not pharmaceutical, systems. Thus, their testing procedures must be verified to meet the *USP* requirements stated in the individual monograph for the component being tested. For example, under *Dextrose Injection*, the following is stated: It contains not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_6H_{12}O_6 \cdot H_2O$. The hospital or institutional chemistry laboratories have to validate their methods to apply to this range and correct for their typical measurement of anhydrous dextrose versus dextrose monohydrate. Similar ranges and issues exist, for example, for injections of calcium gluconate, magnesium sulfate, potassium chloride, and so forth. The critical point is the use of *USP* references and possible laboratory procedural differences.

Precision

The intermediate precision of the ACD can be determined on the basis of the day-to-day variations in performance of the accuracy measures. Thus, the pharmacist must keep a daily record of the above-described accuracy assessments and review the results over time. This review must occur at least at weekly intervals to avoid potentially clinically significant cumulative errors over time. This is especially true for additives with a narrow therapeutic index, such as potassium chloride.●4

Change to read:

FINISHED •PREPARATION ●4 RELEASE CHECKS AND TESTS

All •high-risk level CSPs for administration by injection into the vascular and central nervous systems that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, and vials), or in multiple dose vials for administration to multiple patients, or are exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized are tested to ensure that they are sterile (see *Sterility Tests* ⟨71⟩) and do not contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩). All CSPs that are intended to be solutions must be visually examined for the presence of particulate matter and not administered or dispensed when such matter is observed. The prescription orders, written compounding procedure, preparation records, and expended materials used to make CSPs in all contamination risk levels are inspected for accuracy of correct identities and amounts of ingredients, aseptic mixing and sterilization, packaging, labeling, and expected physical appearance before they are administered or dispensed.●4

Physical Inspection

•Finished CSPs are individually inspected in accordance with written procedures after compounding. If not distributed promptly, these products are individually inspected just prior to leaving the storage area. Those products that are not immediately distributed are stored in an appropriate location as described in the written procedures.●4 Immediately after compounding and as a condition of release, each product unit, where possible, should be inspected against lighted white •or black background or both●4 for evidence of visible particulates or other foreign matter. Pre-release inspection •also includes●4 container–closure integrity and any other apparent visual defect. Products with observed defects should be immediately discarded or marked and segregated from acceptable products in a manner that prevents their administration. When products are not distributed promptly after preparation, a predistribution inspection •is●4 conducted to ensure that a CSP with defects, such as precipitation, cloudiness, and leakage, which may develop between the time of release and the time of distribution, is not released.

Compounding Accuracy Checks

Written procedures for double-checking compounding accuracy •must be followed for every CSP during preparation and immediately●4 prior to release. The double check system should meet state regulations and include label accuracy and accuracy of the addition of all drug products or ingredients used to prepare the finished product and their volumes or quantities. The used additive containers and, for those additives for which the entire container was not expended, the syringes used to measure the additive, should be quarantined with the final products until the final product check is completed. •Compounding personnel must visually confirm that ingredients measured in syringes match the written order being compounded. Preferably, a person other than the compounder can verify that correct volumes of correct ingredients were measured to make each CSP. For example, compounding personnel would pull the syringe plunger back to the volume measured

When practical, confirm accuracy of measurements by weighing a volume of the measured fluid, then calculating that volume by dividing the weight by the accurate value of the density, or specific gravity, of the measured fluid. Correct density or specific gravity values programmed in automated compounding devices, which measure by weight using the quotient of the programmed volume divided by the density or specific gravity, must be confirmed to be

accurate before and after delivering volumes of the liquids assigned to each channel or port. These volume accuracy checks and the following additional safety and accuracy checks in this section must be included in the standard operating procedures manual of the CSP facility.●4

Sterility Testing

•All high-risk level CSPs for administration by injection into the vascular and central nervous systems that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, vials), or in multiple dose vials for administration to multiple patients, or exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized must be tested to ensure that they are sterile (see *Sterility Tests* ⟨71⟩) before they are dispensed or administered. The *Membrane Filtration* method is the method of choice where feasible (e.g., components are compatible with the membrane). A method not described in the USP may be used if verification results demonstrate that the alternative is at least as effective and reliable as the USP *Membrane Filtration* method or the USP *Direct Inoculation of the Culture Medium* method where the membrane filtration method is not feasible.

In such a case, a written procedure requiring daily observation of the media and requiring an immediate recall if there is any evidence of microbial growth must be available. In addition, the patient and the physician of the patient to whom a potentially contaminated CSP was administered is notified of the potential risk. Positive sterility test results should prompt a rapid and systematic investigation of aseptic technique, environmental control, and other sterility assurance controls to identify sources of contamination and correct problems in the methods or processes.●4

•Bacterial Endotoxin (Pyrogen) Testing●4

•All high-risk level CSPs for administration by injection into the vascular and central nervous systems that are prepared in groups of more than 25 identical individual single-dose packages (such as ampuls, bags, syringes, vials), or in multiple dose vials for administration to multiple patients, or exposed longer than 12 hours at 2° to 8° and longer than 6 hours at warmer than 8° before they are sterilized must be tested to ensure that they do not contain excessive bacterial endotoxins (see *Bacterial Endotoxins Test* ⟨85⟩). In the absence of a bacterial endotoxins limit in the official monograph or other CSP formula source, the CSP must not exceed the amount of USP Endotoxin Units (EU per hour per kg of body weight or m^2 of body surface area) specified in the above chapter for the appropriate route of administration.●4

•Identity and Strength Verification of Ingredients

Compounding facilities must have at least the following written procedures for verifying the correct identity and quality of CSPs before they are dispensed and administered:

1. That labels of CSPs bear correct names and amounts or concentrations of ingredients; the total volume; the beyond-use date; the appropriate route(s) of administration; the storage conditions; and other informationfor safe use.
2. That there are correct identities, purities, and amounts of ingredients by comparing the original written order to the written compounding record for the CSP.
3. That correct fill volumes in CSPs and correct quantities of filled units of the CSPs were obtained. When the strength of finished CSPs cannot be confirmed to be accurate, based on the above three inspections, the CSPs must be assayed by methods that are specific for the active ingredients.

To inhibit microbial growth from undetected contamination, finished CSPs that will not be immediately dispensed and administered must be refrigerated at 2° to 8°, unless their chemical and physical stability are known to be adversely affected by cold temperatures. When CSPs are filled into patient-worn infusion devices that are likely to attain temperatures exceeding 30° for more than 24 hours, the chemical and physical stability at such temperatures and durations must be confirmed from either appropriate literature sources or direct testing.●4

Change to read:

STORAGE AND BEYOND-USE DATING

•Beyond-use dates for compounded preparations are usually assigned based on professional experience, which should include careful interpretation of appropriate information sources for the same or similar formulations (see *Stability Criteria and Beyond-Use Dating* in the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩). Beyond-use dates for CSPs are rarely based on preparation-specific chemical assay results, which are used with the Arrhenius equation to determine expiration dates (see *General Notices and Requirements*) for manufactured products. The majority of CSPs are aqueous solutions in which hydrolysis of dissolved ingredients is the most common chemical degradation reaction. The extent of hydrolysis and other heat-catalyzed degradation reactions at any particular time point in the life of a CSP represents the thermodynamic sum of exposure temperatures and durations. Such lifetime stability exposure is represented in the mean kinetic temperature calculation (see *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩). Drug hydrolysis rates increase exponentially with arithmetic temperature increase; thus, exposure of a beta-lactam antibiotic solution for one day at controlled room temperature (see *General Notices and Requirements*) will have an equivalent effect on the extent of hydrolysis of approximately 3 to 5 days in cold temperatures (see *General Notices and Requirements*).

Personnel who prepare, dispense, and administer CSPs must store them strictly in accordance with the conditions stated on the label of ingredient products and finished CSPs. When CSPs are known to have been exposed to temperatures warmer than the warmest labeled limit, but not exceeding 40° (see *General Notices and Requirements*) for more than 4 hours, such CSPs should be discarded, unless appropriate documentation or direct assay data confirms their continued stability.●4

Determining Beyond-Use Dates

•When CSPs deviate from conditions in the approved labeling of manufactured products contained in CSPs, compounding personnel may consult the manufacturer of particular products for advice on assigning beyond-use dates based on chemical and physical stability parameters. Beyond-use dates for CSPs that are prepared strictly in accordance with manufacturers' product labeling must be those specified in that labeling, or from appropriate literature sources or direct testing. Beyond-use dates for CSPs that lack justification from either appropriate literature sources or by direct testing evidence must be assigned as described in the section *Stability Criteria and Beyond-Use Dating* in the general test chapter *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩.

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In addition, the pharmacist may refer to applicable publications to obtain relevant stability, compatibility, and degradation information regarding the drug or its congeners. When assigning a beyond-use date, pharmacists should consult and apply drug-specific and general stability documentation and literature where available, and they should consider the nature of drug and its degradation mechanism, the container in which it is packaged, the expected storage conditions, and the intended duration of therapy (see *Expiration Date and Beyond-Use Date* under *Labeling* in the *General Notices and Requirements*). Stability information must be carefully interpreted in relation to the actual compounded formulation and conditions for storage and use. Predictions based on other evidence, such as publications, charts, tables, and so forth would result in theoretical beyond-use dates. Theoretically predicted beyond-use dating introduces varying degrees of assumptions, and hence a likelihood of error or at least inaccuracy. The degree of error or inaccuracy would be dependent on the extent of differences between the CSP's characteristics (such as composition, concentration of ingredients, fill volume, or container type and material) and the characteristics of the products from which stability data or information are to be extrapolated. The greater the doubt of the accuracy of theoretically predicted beyond-use dating, the greater the need to determine dating periods experimentally. Theoretically predicted beyond-use dating periods should be carefully considered for CSPs prepared from nonsterile bulk active ingredients having therapeutic activity, especially where these CSPs are expected to be compounded routinely. When CSPs will be distributed to and administered in residential locations other than health care facilities, the effect of potentially uncontrolled and unmonitored temperature conditions must be considered when assigning beyond-use dates. It must be ascertained that CSPs will not be exposed to warm temperatures (see *General Notices and Requirements*) unless the compounding facility has evidence to justify stability of CSPs during such exposure.

It should be recognized that the truly valid evidence of stability for predicting beyond-use dating can be obtained only through product-specific experimental studies. Semi-quantitative procedures, such as thin-layer chromatography (TLC), may be acceptable for many CSPs. However, quantitative stability-indicating assays, such as high performance liquid chromatographic (HPLC) assays, would be more appropriate for certain CSPs. Examples include CSPs with a narrow therapeutic index, where close monitoring or dose titration is required to ensure therapeutic effectiveness and to avoid toxicity; where a theoretically established beyond-use dating period is supported by only marginal evidence; or where a significant margin of safety cannot be verified for the proposed beyond-use dating period. In short, because beyond-use dating periods established from product-specific data acquired from the appropriate instrumental analyses are clearly more reliable than those predicted theoretically, the former approach is strongly urged to support dating periods exceeding 30 days.

To ensure consistent practices in determining and assigning beyond-use dates, the pharmacy should have written policies and procedures governing the determination of the beyond-use dates for all compounded products. When attempting to predict a theoretical beyond-use date, a compounded or an admixed product should be considered as a unique system that has physical and chemical properties and stability characteristics that differ from its components. For example, antioxidant, buffering, or antimicrobial properties of a sterile vial for injection (SVI) might be lost upon its dilution, with the potential of seriously compromising the chemical stability of the SVIs active ingredient or the physical or microbiological stability of the SVI formulation in general. Thus, the properties stabilized in the SVI formulation usually cannot be expected to be carried over to the compounded or admixed product. Product-specific, experimentally determined stability data evaluation protocols are preferable to published stability information. Pharmacists should consult the general information chapter *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩ for the appropriate stability parameters to be considered when initiating or evaluating a product-specific stability study.

Compounding personnel who assign beyond-use dates to CSPs when lacking direct chemical assay results must critically interpret and evaluate the most appropriate available information sources to decide a conservative and safe beyond-use date. The standard operating procedures manual of the compounding facility and each specific CSP formula record must describe the general basis used to assign the beyond-use date and storage conditions.

If multiple-dose parenteral medication vials (MDVs) are used, refrigerate the MDVs after they are opened unless otherwise specified by the manufacturer. Discard the MDVs when empty, when suspected or visible contamination occurs, or when the manufacturer's stated expiration date is reached, provided the manufacturers storage conditions have been adhered to. Expiration dating not specifically referenced in the package insert should not exceed 30 days once the vial has been opened.•4

Monitoring Controlled Storage Areas

To ensure that product potency is retained through the manufacturer's labeled expiration date, pharmacists must monitor the drug storage areas within the pharmacy. Controlled temperature storage areas in the pharmacy (refrigerators, 2° to 8°; freezers, –20° to –10°; and incubators, 30° to 35°; etc.) should be monitored at least once daily and the results documented on a temperature log. Additionally, pharmacy personnel should note the storage temperature when placing the product into or removing the product from the storage unit in order to monitor any temperature aberrations. Suitable temperature recording devices may include a calibrated continuous recording device or an NBS calibrated thermometer that has adequate accuracy and sensitivity for the intended purpose and should be properly calibrated at suitable intervals. If the pharmacy uses a continuous temperature recording device, pharmacy personnel should verify at least once daily that the recording device itself is functioning properly.

The temperature sensing mechanisms should be suitably placed in the controlled temperature storage space to reflect accurately its true temperature. In addition, the pharmacy should adhere to appropriate procedures of all controlled storage spaces to ensure that such spaces are not subject to significantly prolonged temperature fluctuations as may occur, for example, by leaving a refrigerator door open too long.

Change to read:

MAINTAINING PRODUCT QUALITY AND CONTROL AFTER •THE CSP•4 LEAVES THE PHARMACY

•Sterile Preparations for Institutional Use

This section pertains to the responsibilities of the pharmacy for maintaining product quality and control after the CSP leaves the pharmacy for distribution and use within the organized health care system to which the pharmacy belongs. The pharmacy is responsible for the quality of all CSPs prepared by or dispensed from the pharmacy, throughout the life cycle of the CSP, regardless of where the CSP exists physically within the organized health care system. In fulfilling this general responsibility, the pharmacy is responsible for the proper packaging, handling, transport, and storage of CSPs prepared by or dispensed from it, including the appropriate education, training, and supervision of pharmacy personnel assigned to these functions. The pharmacy should assist in the education and training of nonpharmacy personnel responsible for carrying out any aspect of these functions.

Establishing, maintaining, and assuring compliance with comprehensive written policies and procedures encompassing these responsibilities is a further responsibility of the pharmacy. Where nonpharmacy personnel are assigned tasks involving any of these responsibilities, the policies and procedures encompassing those tasks should be developed by the pharmacy in consultation with other institutional departments as appropriate. Activities or concerns that should be addressed as the pharmacy fulfills these responsibilities are as follows.

PACKAGING, HANDLING, AND TRANSPORT

Inappropriate processes or techniques involved with packaging, handling, and transport can adversely affect product quality and package integrity. While pharmacy personnel routinely perform many of the tasks associated with these functions, some tasks, such as transport, handling, and placement into storage, may be fulfilled by nonpharmacy personnel who are not under the direct administrative control of the pharmacy. Under these circumstances, appropriate written policies and procedures are established by the pharmacy with the involvement of other departments or services whose personnel are responsible for carrying out those CSP-related functions for which the pharmacy has a direct interest. The performance of the nonpharmacy personnel is monitored for compliance to established policies and procedures.

The critical requirements that are unique to CSPs and that are necessary to ensure product quality and packaging integrity must be addressed in written procedures. For example, techniques should be specified to prevent the depression of syringe plungers or dislodging of syringe tips during handling and transport. Additionally, disconnection of system components (for example, where CSPs are dispensed with administration sets attached to them) must be prevented throughout the life cycle of the product. Foam padding or inserts are particularly useful where CSPs are transported by pneumatic tube systems. Regardless of the methods used, the pharmacy has to evaluate their effectiveness and the reliability of the intended protection. Evaluation should be continuous, for example, through a surveillance system, including a system of problem reporting to the pharmacy.

Inappropriate transport and handling can adversely affect the quality of certain CSPs having unique stability concerns. For example, the physical shaking that might occur during pneumatic tube transport, or undue exposure to heat or light, have to be addressed on a product-specific basis. Alternate transport modes or special packaging measures might be needed for the proper assurance of quality of these CSPs. The use of tamper-proof closures and seals on CSP ports can add an additional measure of security to ensure product integrity regardless of transport method used.

Chemotoxic and other hazardous CSPs require safeguards to maintain the integrity of the CSP and to minimize the exposure potential of these products to the environment and to personnel who may come in contact with them. Special requirements associated with the packaging, transport, and handling of these agents include the prevention of accidental exposures or spills and the training of personnel in the event of an exposure or spill. Examples of special requirements of these agents also include exposure-reducing strategies such as the use of Luer lock syringes and connections, syringe caps, the capping of container ports, sealed plastic bags, impact-resistant containers, and cautionary labeling. Appropriate cushioning for pneumatic tube transport should be selected and evaluated to ensure that the products so conveyed can withstand the stresses induced by the system. Pneumatic transport of nonevaluated packaging alternatives should be avoided. Additional references should be consulted as necessary for further information on handling chemotoxic and other hazardous drugs.

USE AND STORAGE

The pharmacy is responsible for ensuring that CSPs in the patient-care setting maintain their quality until administered. The immediate labeling of the CSP container will display prominently and understandably the requirements for proper storage and expiration dating. Delivery and patient-care-setting personnel must be properly trained to deliver the CSP to the appropriate storage location. Outdated and unused CSPs must be returned to the pharmacy for disposal or possible reuse.

Written procedures have to exist to ensure that storage conditions in the patient-care setting are suitable for the CSP-specific storage requirements. Procedures include daily monitoring and documentation of drug storage refrigerators to ensure temperatures between 2° and 8° and the monthly inspection of all drug storage locations by pharmacy personnel. Inspections must confirm compliance with appropriate storage conditions, separation of drugs and food, proper use of multiple-dose containers, and the avoidance of using single-dose products as multiple-dose containers. CSPs, as well as all other drug products, must be stored in the patient-care area in such a way as to secure them from unauthorized personnel, visitors, and patients.

ADMINISTRATION

Procedures essential for generally ensuring product quality, especially sterility assurance, when readying a CSP for its subsequent administration include proper hand-washing, aseptic technique, site care, and change of administration sets. Additional procedures may also be essential for certain products, devices, or techniques. Examples where such special procedures are needed include in-line filtration, the operation of automated infusion control devices, and the replenishment of drug products into the reservoirs of implantable or portable infusion pumps.

REDISPENSED CSPS

The pharmacy must have the sole authority for determining whether a CSP not administered as originally intended can be used for an alternate patient or under alternate conditions. All CSPs that are not used as originally intended must be returned to the pharmacy for appropriate disposition, which may include redispensing, but only if adequate continuing quality can be fully ensured. The following may provide such assurance: the CSP was maintained under continuous refrigeration and protected from light, if required; no evidence of tampering or any readying for use outside the pharmacy exists; and there is sufficient time remaining until the originally assigned beyond-use time and date will be reached. Thus, initial preparation and thaw times should be documented and reliable measures should have been taken to prevent and detect tampering. Compliance with all procedures associated with maintaining product quality is essential. The CSP must not be redispensed if there is not adequate assurance that product quality and packaging integrity (including the connections of devices, where applicable) were continuously maintained between the time the CSP left and the time that it was returned to the pharmacy. Additionally, CSPs must not be redispensed if redispensing cannot be supported by the originally assigned beyond-use time.

EDUCATION AND TRAINING

The assurance of CSP quality and packaging integrity is highly dependent upon the proper adherence of all personnel to the pertinent written procedures. The pharmacy must design, implement, and maintain a formal education, training, and competency assessment program that encompasses all the functions and tasks addressed in the foregoing sections and all personnel to whom such functions and tasks are assigned. This program includes the assessment and documentation of procedural breaches, administration mishaps, side effects, allergic reactions, and complications associated with dosage or administration, such as extravasation. This program should be coordinated with the institution's adverse-event and incident reporting programs.●4

•Packing and Transporting CSPs

The following sections on *Packing CSPs for Transit* and *Transit of CSPs* describe how to maintain sterility and stability of CSPs until they are delivered to patient care locations for administration.

PACKING CSPS FOR TRANSIT

When CSPs are distributed to locations outside the premises in which they are compounded, compounding personnel select packing containers and materials that are expected to maintain physical integrity, sterility, and stability of CSPs during transit. Packing is selected that simultaneously protects CSPs from damage, leakage, contamination, and degradation; and protects personnel who transport packed CSPs from harm. The standard operating procedures manual of the compounding facility specifically describes appropriate packing containers and insulating and stuffing materials, based on information from product specifications, vendors, and experience of compounding personnel. Written instructions that clearly explain how to safely open containers of packed CSPs are provided to patients and other recipients.

TRANSIT OF CSPS

Compounding facilities that ship CSPs to locations outside their own premises must select modes of transport that are expected to deliver properly packed CSPs in undamaged, sterile, and stable condition to recipients.

Compounding personnel should ascertain that temperatures of CSPs during transit by the selected mode will not exceed the warmest temperature specified on the storage temperature range on CSPs labels. It is recommended that compounding personnel communicate directly with the couriers to learn shipping durations and exposure conditions that CSPs may encounter.

Compounding personnel must include specific handling and exposure instructions on the exteriors of containers packed with CSPs to be transported and obtain reasonable assurance of compliance therewith from transporters. Compounding personnel must periodically review the delivery performance of couriers to ascertain that CSPs are being efficiently and properly transported.

STORAGE IN LOCATIONS OUTSIDE CSP FACILITIES

Compounding facilities that ship CSPs to patients and other recipients outside their own premises must ascertain or provide, whichever is the appropriate case, the following assurances:

1. Labels and accessory labeling for CSPs include clearly readable beyond-use dates, storage instructions, and disposal instructions for out-of-date units.
2. Each patient or other recipient is able to store the CSPs properly, including the use of a properly functioning refrigerator and freezer if CSPs are labeled for such storage.●4

Change to read:

PATIENT OR CAREGIVER TRAINING

A formal training program •is●4 provided as a means to ensure understanding and compliance with the many special and complex responsibilities placed upon the patient or caregiver for the storage, handling, and administration of •CSPs.●4 The instructional objectives for the training program •includes●4 all home care responsibilities expected of the patient or caregiver and •is●4 specified in terms of patient or caregiver competencies.

Upon the conclusion of the training program, the patient or caregiver should, correctly and consistently, be able to do the following:

(1) Describe the therapy involved, including the disease or condition for which the •CSP●4 is prescribed, goals of therapy, expected therapeutic outcome, and potential side effects of the •CSP.●4
(2) Inspect all drug products, devices, equipment, and supplies on receipt to ensure that proper temperatures were maintained during transport and that goods received show no evidence of deterioration or defects.
(3) Handle, store, and monitor all drug products and related supplies and equipment in the home, including all special requirements related to same.
(4) Visually inspect all drug products, devices, and other items the patient or caregiver is required to use immediately prior to administration in a manner to ensure that all items are acceptable for use. For example, •CSPs must●4 be free from leakage, container cracks, particulates, precipitate, haziness, discoloration, or other deviations from the normal expected appearance, and the immediate packages of sterile devices •must be●4 completely sealed with no evidence of loss of package integrity.
(5) Check labels immediately prior to administration to ensure the right drug, dose, patient, and time of administration.
(6) Clean the in-home preparation area, scrub hands, use proper aseptic technique, and manipulate all containers, equipment, apparatus, devices, and supplies used in conjunction with administration.
(7) Employ all techniques and precautions associated with •CSP●4 administration, for example, preparing supplies and equipment, handling of devices, priming the tubing, and discontinuing an infusion.
(8) Care for catheters, change dressings, and maintain site patency as indicated.
(9) Monitor for and detect occurrences of therapeutic complications such as infection, phlebitis, electrolyte imbalance, and catheter misplacement.
(10) Respond immediately to emergency or critical situations such as catheter breakage or displacement, tubing disconnection, clot formation, flow blockage, and equipment malfunction.

(11) Know when to seek and how to obtain professional emergency services or professional advice.
(12) Handle, contain, and dispose of wastes, such as needles, syringes, devices, biohazardous spills or residuals, and infectious substances.

Training programs •include a•4 hands-on demonstration and practice with actual items that the patient or caregiver is expected to use, such as •CSP•4 containers, devices, and equipment. The patient or caregiver •practices•4 aseptic and injection technique under the direct observation of a health professional.

The pharmacy, in conjunction with nursing or medical personnel, is responsible for ensuring initially and on an ongoing basis that the patient or caregiver understands, has mastered, and is capable of and willing to comply with all of these home care responsibilities. This •is•4 achieved through a formal, written assessment program. All specified competencies in the patient or caregiver's training program •are•4 formally assessed. The patient or caregiver •is•4 expected to demonstrate to appropriate health care personnel their mastery of their assigned activities before being allowed to administer •CSPs•4 unsupervised by a health professional.

Printed material such as checklists or instructions provided during training may serve as continuing post-training reinforcement of learning or as reminders of specific patient or caregiver responsibilities. Post-training verbal counseling •can•4 also be used periodically, as appropriate, to reinforce training and to ensure continuing correct and complete fulfillment of responsibilities.

Delete the following:

•PATIENT MONITORING AND COMPLAINT SYSTEM

The pharmacy must have written policies and procedures describing the monitoring of patients using CSPs and the handling of reports of adverse events.

Outcome Monitoring

The pharmacy is responsible for developing a patient monitoring plan, which includes written outcome measures and systems for routine patient assessment. The outcome monitoring system should provide information suitable for the evaluation of the quality of patient care and of pharmaceutical services. Examples of assessment parameters include infection rates, rehospitalization rates, incidence of adverse drug reactions, catheter complications, and other variables that may serve as meaningful indicators of the effectiveness and suitability of the home use of CSPs. In selecting suitable outcome measures, the focus should be on high-risk, high-volume, or problem-prone factors.

Reports

The pharmacy should have policies and procedures for the receipt, documentation, handling, and disposition of reports of patient problems, complaints, adverse drug reactions, drug product or device defects, and other adverse events reported by patients, caregivers, family members, pharmacists, or other health professionals. The pharmacy should have a procedure to ensure that the patient receives prompt and appropriate medical attention as necessary in response to all adverse incidents from CSPs or devices. When a complaint or problem prompts a suspicion that a CSP or a device may be defective, the pharmacy should also be able to identify and recall the potentially defective item to the patient level whenever appropriate.

Procedures should also include a mechanism for periodic review of reports received to determine any need for correction of underlying systems problems. All reports received should be maintained for a reasonable period of time in a log, file, or binder dedicated for this purpose and readily retrievable as needed for subsequent analysis, legal or regulatory inquiry, or quality assurance audit. Standardized forms or formats for the reporting and recording of incidents, complaints, and so forth should be used. Reports should be completed and signed by the individual receiving it or by the individual involved in the situation. Procedures should depict the classification, documentation, investigation, and resolution of all reports and should provide a mechanism for participation in various federal and state reporting programs such as USP or FDA programs for reporting reaction problems, or defects with drug products or medical devices.•4

Add the following:

•PATIENT MONITORING AND ADVERSE EVENTS REPORTING

Compounding facilities must clinically monitor patients treated with CSPs according to the regulations and guidelines of their respective state health care practitioner licensure boards or of accepted standards of practice. Compounding facilities must provide patients and other recipients of CSPs with a way to address their questions and report any concerns that they may have with CSPs and their administration devices.

The standard operating procedures manuals of compounding facilities must describe specific instructions for receiving, acknowledging, and dating receipts; and for recording, or filing, and evaluating reports of adverse events and of the quality of preparation claimed to be associated with CSPs. Reports of adverse events with CSPs must be reviewed promptly and thoroughly by compounding supervisors to correct and prevent future occurrences. Compounding personnel are encouraged to participate in adverse event reporting and product defects programs of the Food and Drug Administration (FDA) and United States Pharmacopeia (USP).•4

Change to read:

THE QUALITY ASSURANCE PROGRAM

A provider of •CSPs must•4 have in place a formal Quality Assurance (QA) Program[4] intended to provide a mechanism for monitoring, evaluating, correcting, and improving the activities and processes described in this chapter. Emphasis in the QA Program is•4 placed on maintaining and improving the quality of systems and the provision of patient care. In addition, the QA program ensures•4 that any plan aimed at correcting identified problems also includes appropriate follow-up to make certain that effective corrective actions were performed.[5]

Characteristics of a QA plan include the following:

(1) Formalization in writing;
(2) Consideration of all aspects of the preparation and dispensing of products as described in this chapter, including environmental testing, validation results, etc.;
(3) Description of specific monitoring and evaluation activities;
(4) Specification of how results are to be reported and evaluated;
(5) Identification of appropriate follow-up mechanisms when action limits or thresholds are exceeded;and
(6) Delineation of the individuals responsible for each aspect of the QA program.

In developing a specific plan, focus •is•4 on establishing objective, measurable indicators for monitoring activities and processes that are deemed high-risk, high-volume, or problem-prone. Appropriate evaluation of environmental monitoring might include, for example, the trending of an indicator such as settling plate counts. In general, the selection of indicators and the effectiveness of the overall QA plan •is•4 reassessed on an annual basis.

[4] Other accepted terms that describe activities aimed at assessing and improving the quality of care rendered include Continuous Quality Improvement, Quality Assessment and Improvement, and Total Quality Management.

[5] The use of additional resources, such as the Accreditation Manual for Home Care from the Joint Commission on Accreditation of Healthcare Organizations, may prove helpful in the development of a QA plan.

•APPENDIX

CRITERIA	LOW-RISK LEVEL	MEDIUM-RISK LEVEL	HIGH-RISK LEVEL
Compounding Conditions	• Compounded entirely under ISO Class 5 (Class 100) conditions • Compounding involves only transfer, measuring, and mixing manipulations with closed or sealed packaging systems that are performed promptly and attentively • Manipulations are limited to aseptically opening ampuls, penetrating sterile stoppers on vials with sterile needles and syringes and transferring sterile liquids in sterile syringes to sterile administration devices and packages of other sterile products	• All conditions listed under low-risk level • Multiple individual or small doses of sterile products are combined or pooled to prepare a CSP that will be administered either to multiple patients or to one patient on multiple conditions • Compounding process includes complex aseptic manipulations other than the single-volume transfer • Compounding process requires unusually long duration • The sterile CSPs do not contain broad-spectrum bacteriostatic agents, and are administered over several days	• Nonsterile ingredients are incorporated or a nonsterile device is employed before terminal sterilization • Sterile ingredients, components, devices and mixtures are exposed to air quality inferior to ISO Class 5 (Class 100) • Nonsterile preparations are exposed for not more than 6 hours before being sterilized • Nonsterile preparations are terminally sterilized but are not tested for bacterial endotoxins • It is assumed that the chemical purity and content strength of ingredients meet their original or compendial specifications in unopened or in opened packages of bulk ingredients
QA Program	• Formalized in writing • Describes specific monitoring and evaluation activities • Reporting and evaluation of results • Identification of follow-up activities when thresholds are exceeded • Delineation of individual responsibilities for each aspect of the program	See low-risk level.	See low-risk level.
QA Practices	• Routine disinfection and quality testing of direct compounding environment • Visual confirmation of personnel processes regarding gowning, etc. • Review of orders and packages of ingredients to assure correct identity and amounts of ingredients • Visual inspection of CSP • Media-fill test procedure performed at least annually for each person	See low-risk level.	See low-risk level.
Outcome Monitoring	Yes	Yes	Yes

APPENDIX *(continued)*

CRITERIA	LOW-RISK LEVEL	MEDIUM-RISK LEVEL	HIGH-RISK LEVEL
Reports/Documents	• Written policies and procedures • Adverse event reporting • Complaint procedures • Periodic review of quality control documents	See low-risk level.	See low-risk level.
Patient and Caregiver Training	• Formalized program that includes — Understanding of the therapy provided — Handling and storage of the CSP — Appropriate administration techniques — Use and maintenance of any infusion device involved — Use of printed material — Appropriate follow-up	See low-risk level.	See low-risk level.
Maintaining Product Quality and Control once the CSP leaves the Pharmacy (both institutional based and NICPs)	• Packaging, handling, and transport — Written policies and procedures including the packaging, handling, and transport of chemotoxic/hazardous CSPs • Use and storage — Written policies and procedures • Administration — Written polices and procedures dealing with such issues as handwashing, aseptic technique, site care, etc. • Education/Training — Written policies and procedures dealing with proper education of patients and caregivers ensuring all of the above	See low-risk level.	See low-risk level.
Storage and Beyond-Use Dating	• Specific labeling requirements • Specific beyond-use dating policies, procedures, and requirements • Policies regarding storage	See low-risk level.	See low-risk level.
Storage Conditions and Beyond-Use Dating for completed CSP	In the absence of sterility testing, storage periods (before administration) shall not exceed the following:		
	Room temperature ≤48 hours 2°–8° ≤14 days ≤20 ° ≤45 days	Room temperature ≤30 hours 2°–8° ≤7 days ≤20 ° ≤45 days	Room temperature ≤24 hours 2°–8° ≤3 days ≤20 ° ≤45 days

APPENDIX *(continued)*

CRITERIA	LOW-RISK LEVEL	MEDIUM-RISK LEVEL	HIGH-RISK LEVEL
Finished Product-Release Checks and Tests	• Written policies and procedures that address — Physical inspections — Compounding accuracy checks	See low-risk level.	See low-risk level.
Finished Product-Release Checks and Tests	• Written policies and procedures that address — Sterility testing — Pyrogen testing — Potency testing	See low-risk level.	See low-risk level.
CSP Work Environment	• Appropriate solid surfaces • Limited (but necessary) furniture, fixtures, etc. • Anteroom area • Buffer zone	See low-risk level.	See low-risk level.
Equipment	• Written policies and procedures that address calibration, routine maintenance, personnel training	See low-risk level.	See low-risk level.
Components	• Written policies and procedures that address Sterile components	See low-risk level.	Sterile and nonsterile drug components must meet the compendial standards if available • Written policies and procedures that address — Sterile components — Nonsterile components
Processing: Aseptic Technique	• Written policies and procedures that address specific training and performance evaluation • Critical operations are carried out in a Direct Compounding Common Area (DCCA)	See low-risk level.	See low-risk level.
Environmental Control	• Policies and procedures that address — Cleaning and sanitizing the workspaces (DCCA) — Personnel and gowning — Standard operating procedures	See low-risk level.	See low-risk level.
Verification Procedures • Sterility Testing	Not required	Not required	Yes, recommended

APPENDIX *(continued)*

CRITERIA	LOW-RISK LEVEL	MEDIUM-RISK LEVEL	HIGH-RISK LEVEL
Verification Procedures • Environmental Monitoring	• Certification of LAFW and barrier isolates every six (6) months • Certification of the buffer room/zone and anteroom/zone every six (6) months • Bacterial monitoring using an appropriate manner at least monthly	See low-risk level.	See low-risk level.
Verification Procedures • Personnel Training and Education	Initially and annually thereafter • Didactic review • Written testing • Media-fill testing	See low-risk level.	See low-risk level.

(Official January 1, 2004)●4

Add the following:

•⟨1196⟩ PHARMACOPEIAL HARMONIZATION

This general information chapter provides information about the concept of harmonization by the Pharmacopeial Discussion Group (PDG). The chapter provides: (1) the *PDG Policy Statement*; (2) the *PDG Working Procedures*; (3) a discussion; (4) a status report; and (5) a glossary.

HARMONIZATION POLICY

The following policy statement was concluded by the PDG at its September 2002 meeting.

General Information

In 1989, the PDG was formed with representatives from the European Directorate for the Quality of Medicines in the Council of Europe, the United States Pharmacopeial Convention, Inc., and the Japanese Pharmacopoeia in the Ministry of Health and Welfare—now the Ministry of Health, Labor, and Welfare (MHLW). Since that time, the PDG generally meets twice a year to work on pharmacopeial harmonization topics. In May 2001, the PDG welcomed the World Health Organization as an observer. While not part of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the PDG usually meets in conjunction with the ICH and provides the ICH Steering Committee with reports of its progress. To facilitate harmonization of some ICH Quality guidelines and the Quality section of the Common Technical Document, the PDG representatives sometimes attend ICH expert working group discussions as observers.

Purpose

A pharmacopeial monograph for an active ingredient or excipient, preparation, or other substance used in the manufacture or compounding of a medicinal product generally provides a name, definition, description, and sometimes packaging, labeling, and storage statements. Thereafter, the monograph provides tests, procedures, and acceptance criteria that constitute the specification. For frequently cited procedures, a monograph may refer to a general chapter for editorial convenience. The PDG works to harmonize excipient monographs and general chapters. This will reduce manufacturers' burden of performing analytical procedures in different ways, using different acceptance criteria. At all times, the PDG works to maintain an optimal level of science consistent with protection of the public health.

Definition of Harmonization

The PDG has defined harmonization of a pharmacopeial monograph or general chapter as follows:

"A pharmacopeial general chapter or other pharmacopeial document is harmonized when a pharmaceutical substance or product tested by the document's harmonized procedure yields the same results and the same accept/reject decision is reached."

When using a fully harmonized pharmacopeial monograph or general chapter, an analyst will perform the same procedures and reach the same accept/reject decisions irrespective of which PDG pharmacopeia is referenced. This approach is called interchangeability, and each pharmacopeia will identify, in an appropriate manner, such a monograph or general chapter.

When full harmonization of a pharmacopeial monograph or general chapter is not possible, the PDG works to harmonize it using an approach termed harmonization by attribute. According to this approach, some elements of a monograph or general chapter may be harmonized, but others may not. When a monograph is harmonized by attribute, a combination of approaches is needed. For nonharmonized elements, reliance on the individual PDG pharmacopeia is needed.

Process

Harmonization of pharmacopeial documents in the PDG occurs based upon decisions of the expert bodies of each pharmacopeia. The PDG works transparently in many ways, including, principally through the public notice and comment procedures of each pharmacopeia. The details are described below under *PDG Working Procedures*.

Implementation

The implementation of a harmonized document varies in the three PDG regions, depending upon their legal requirements, need of translation, and publication schedules. Each pharmacopeia generally allows some period of time after publication to implement official harmonized texts to allow manufacturers and other users to achieve conformity. Harmonization is not achieved until the text becomes official in all three pharmacopeias.

Revision of Harmonized Monographs

The pharmacopeias participating in the PDG have agreed not to revise unilaterally any harmonized document after publication. Should revisions be necessary for any appropriate reasons, the initiating pharmacopeia notifies the PDG, and revision proceeds according to the *PDG Working Procedures*.

Change to read:

PDG WORKING PROCEDURES

General

Harmonization may be carried out retrospectively for existing monographs or chapters or prospectively for new monographs or chapters.

The three pharmacopeias have a commitment to respect the agreed working procedures and the associated time deadlines as an essential part of the harmonization procedure.

Harmonization of pharmacopeial documents in the PDG occurs based on decisions of the expert bodies of each pharmacopeia. The PDG works transparently in many ways, including principally through the public notice and comment procedures of each pharmacopeia.

Where necessary, meetings of experts are held to identify potential solutions to resolve difficult problems.

The specific stages of the PDG process involved in harmonization are described below.

Stage 1: Identification

Based on inquiry among its users, the PDG identifies subjects to be harmonized among PDG pharmacopeias and nominates a coordinating pharmacopeia for each subject.

The PDG distributes the work by consensus among the three pharmacopeias and strives for a balance in the distribution of coordinating pharmacopeia assignments.

Stage 2: Investigation

For a subject to be harmonized retrospectively, the coordinating pharmacopeia collects the information on the existing specifications in the three pharmacopeias, on the grades of products marketed, and on the potential analytical procedures.

The coordinating pharmacopeia prepares a draft monograph or chapter, accompanied by a report giving the rationale for the proposal with validation data.

Stage 2 ends with the proposal draft, which is mentioned in this procedure as a Stage 3 draft. The Stage 3 draft, accompanied by supporting comments or data that explain the reasons for each test procedure or limit proposed, is sent by the coordinating pharmacopeia to the secretariats of the other two PDG pharmacopeias.

Stage 3: Proposal for Expert Committee Review

The three pharmacopeias forward the Stage 3 draft to their expert committee (through meetings or consultation by correspondence).

Comments by the experts resulting from this preliminary survey are sent to their respective pharmacopeial secretariat, preferably within 2 months. However, the comment period should not exceed 4 months. Within 2 months of receipt of the comments, the pharmacopeial secretariat should consolidate the comments and forward them to the coordinating pharmacopeia.

The coordinating pharmacopeia reviews the comments received and prepares a harmonized document (Stage 4 draft) accompanied by a commentary discussing comments received regarding the previous text and providing reasons for action taken in response to those comments.

The Stage 4 draft, as far as possible written in global style—a style easily understood by a variety of readers—together with the commentary, are sent to the secretariats of the other pharmacopeias (end of Stage 3).

Stage 4: Official Inquiry

The Stage 4 draft and the commentary are published in the revision document of each pharmacopeia in a section entitled International Harmonization. The draft is published in its entirety.

The corresponding secretariats may have to add information essential to the understanding of the implementation of the texts (e.g., the addition of the description of an analytical procedure or of reagents that do not exist in the pharmacopeia) and a translation is added by the European and Japanese Pharmacopoeias. The style may be adapted to that of the pharmacopeia concerned or global style may be used. The three pharmacopeias endeavor to publish the drafts simultaneously or as closely as possible.

Comments regarding this draft are sent by readers of the revision document to their respective pharmacopeial secretariat, preferably within 4 months, and at most within 6 months of its publication.

Each pharmacopeia analyzes the comments received and submits its consolidated comments to the coordinating pharmacopeia within 2 months of the end of the review/comment period.

The coordinating pharmacopeia reviews the comments received and prepares a draft harmonized document (Stage 5A draft), accompanied by a commentary discussing comments received regarding the previous text and providing reasons for action taken in response to those comments.

The Stage 5A draft together with the commentary is sent to the secretariats of the other two PDG pharmacopeias.

Stage 5. Consensus

5A. PROVISIONAL

The Stage 5A draft is reviewed and commented on by the other two PDG pharmacopeias within 4 months of receipt. The three pharmacopeias shall do their utmost to reach full agreement at this stage to obtain a final consensus document.

If a consensus has not been reached, the coordinating pharmacopeia prepares a revised version (Stage 5A/2), taking relevant, substantiated comments on the Stage 5A document from the two other pharmacopeias into consideration. The revised document (Stage 5A/2), together with the commentary, are sent to the secretariats of the other two PDG pharmacopeias. The revised document is reviewed and commented on by the other two PDG pharmacopeias, preferably within 2 months of receipt. This review/comment and revision process of the 5A document are repeated (Stage 5A/n) until the three PDG pharmacopeias reach a consensus or until the coordinating pharmacopeia considers that harmonization by attribute should be applied.

If the coordinating pharmacopeia considers certain attributes in the monograph or provisions in a general chapter (especially for retroactive harmonization) are such that it will not be possible to harmonize within a reasonable time period, harmonization by attribute will be applied. If harmonization by attribute is applied, a special cover page (see the table in the *Appendix*) indicating harmonization is included with the draft. The text contains only harmonized attributes/provisions; nonharmonized and local attributes are not included. The table is prepared as follows: if three pharmacopeias agree on the attribute, there will be a (+) in all columns; if two pharmacopeias agree that the attribute should be included and have agreed on the method and limit, there will be a (+) in the column for those two pharmacopeias, and a (–) in the column for the pharmacopeia that will not stipulate the test.

For nonharmonized or local requirements, if three pharmacopeias agree that the attribute should be included, but have not come to agreement on the method and/or limit: state attribute under "nonharmonized attributes." If only one pharmacopeia will include an attribute: state under "local requirement."

If the Stage 5A draft is substantially different from the Stage 4 draft, the PDG may decide that it should be published again in the revision documents; the draft then reverts technically to Stage 4, revised.

5B. DRAFT SIGN-OFF

When full agreement is reached, the 5B draft is sent by the coordinating pharmacopeia to the other pharmacopeias no later than 4 weeks before a PDG meeting for final confirmation. The document is then presented for sign-off at the PDG meeting.

NOTE—The last two stages of the implementation of the "harmonized" chapters and monographs take place individually according to the procedures established by each pharmacopeial organization.

Stage 6: Adoption

The document is submitted for adoption to the organization responsible for each pharmacopeia. Each pharmacopeia incorporates the harmonized draft according to its own procedures.

Adopted texts are published by the three pharmacopeias in their supplements, or where applicable, in a new edition.

If necessary, the Stage 5B draft may be adopted with some amendments (local requirements) corresponding to a general policy in the national or regional (European) area. If a pharmacopeia includes a local attribute after the sign-off of a text, it will inform the PDG.

Users of the pharmacopeias are appropriately informed of the harmonization status of monographs and general chapters. In the *European Pharmacopoeia* (*EP*) and *USP-NF*, for general chapters, this is done via a preliminary paragraph. For the *Japanese Pharmacopoeia* (*JP*), a notification is made by MHLW, and information is given in a general chapter.

Stage 7: Implementation

The pharmacopeias will inform each other of the date of implementation in their particular region.

The date of implementation of a harmonized document varies in the three PDG regions depending on their legal requirements, need of translation, and publication schedules. Each pharmacopeia generally allows some period of time after publication for implementation to allow manufacturers and other users to achieve conformity. Harmonization is not achieved until the text becomes official in all three pharmacopeias.

Revision

Following is the procedure for the revision of harmonized monographs and chapters:

The pharmacopeias participating in the PDG have agreed not to revise unilaterally any harmonized document (monograph or chapter) after sign-off or after publication.

A pharmacopeia requesting the revision of a monograph or chapter shall apply the following criteria for justification of the revision:

- Public health and safety reasons.
- Insufficient supply of pharmacopeial-quality product on the market.
- Specified analytical reagents or equipment are not available.
- New methods of preparation of products or reagents are not covered by the current monograph.
- Analytical procedures can be replaced by more appropriate, accurate, or precise procedures.

The PDG as a whole has to agree to initiate the revision. A coordinating pharmacopeia will be nominated. The coordinating pharmacopeia will prepare a Stage 3 draft, based on the validation of data provided by the pharmacopeia requesting the revision.

The *PDG Working Procedures* will then be followed. The revisions of a sign-off document prepared for this or other reasons are indicated as revision 1, 2, 3, etc.

In case of health and safety issues, and whenever agreed to by the PDG, an accelerated procedure shall be applied (shortening and/or eliminating stages).

Discussion

Harmonization of general chapters and monographs benefits manufacturers of pharmaceutical products intended for human use, regulatory agencies, and ultimately, practitioners and patients. Benefits are derived from (1) reduced development effort; (2) simplification of regulatory filings; and (3) reduced release testing.

Pharmacopeial harmonization amplifies the work of the ICH, particularly for Quality topics. While the PDG is not part of the ICH, the PDG periodically provides updates to the ICH Steering Committee, and in the past participated in a joint task force. This task force focused on harmonization of general chapters considered important to the ICH harmonized document *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances (Q6A)*. USP also participates in the International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Products (VICH). As with the ICH, some of the quality guidelines developed in VICH depend upon harmonization of pharmacopeial general chapters. A major difference between the PDG and ICH/VICHs is that the ICH/VICH guidelines generally are applicable only to ingredients and drug products not previously registered in an ICH/VICH region or nation, whereas the PDG harmonization applies to all marketed products in the applicable region or nation.

In the case of harmonization by attribute, nonharmonization or divergence will be indicated in *USP–NF* and *EP* by the symbol ◆. For these nonharmonized attributes, reliance upon the individual pharmacopeia is required. A monograph or general chapter in one PDG pharmacopeia may unilaterally include additional local or national attributes that are not included in the corresponding text of the other pharmacopeias. Such text is not considered by the PDG to be a divergence from the PDG harmonized text.

As with other *USP–NF* revisions, draft harmonization texts are published for comment in *Pharmacopeial Forum*. Final harmonized official text in *USP–NF* is presented in the latest edition, *Supplement*, or *Interim Revision Announcement.* The current status of all harmonization projects appears in Table 1and Table 2. These status tables will be updated in subsequent editions of *USP–NF* and its *Supplements*.

In the U.S., cases of noncompliance and/or dispute are resolved through performance of the official procedure in *USP* or *NF*. If the procedure and its acceptance criteria are harmonized in the PDG, then a manufacturer may follow the relevant compendial instructions in *USP–NF*, *EP*, or *JP*.

Table 1. Status of Harmonization—Excipient Monographs

Excipient Name	Coordinating Pharmacopeia	Harmonization Stage
Alcohol	EP	6
Benzyl Alcohol	EP	6
Dehydrated Alcohol	EP	6
Butyl Paraben	EP	4
Calcium Disodium Edetate	JP	5A2
•Calcium Carbonate	USP	2•4
Calcium Phosphate Dibasic (and anhydrous)	JP	5A
Carboxymethylcellulose Calcium	USP	6
Carboxymethylcellulose Sodium	USP	4
•Carmellose	JP	2•4
Cellulose Acetate	USP	6
Cellulose Acetate Phthalate	USP	6
Microcrystalline Cellulose	USP	4 Revised
Cellulose, Powdered	USP	4 Revised
Citric Acid, Anhydrous	EP	6
Citric Acid, Monohydrate	EP	6
•Copovidone	JP	2•4
Croscarmellulose Sodium	USP	6
Crospovidone	EP	4
Ethyl Cellulose	EP	6
Ethyl Paraben	EP	4
•Gelatin	EP	2•4
•Glucose	EP	2•4
Glycerin	USP	3
•Glyceryl Monostearate	USP	2•4
Hydroxyethyl Cellulose	EP	4
Hydroxypropyl Cellulose	USP	4
Hydroxypropyl Cellulose, Low Substituted	USP	4
Hydroxypropylmethyl Cellulose	JP	4
Hydroxypropylmethyl Cellulose Phthalate	USP	4 Revised
Lactose, Anhydrous	USP	6
Lactose, Monohydrate	USP	6
Magnesium Stearate	USP	5A
•Mannitol	EP	2•4
Methyl Cellulose	JP	4
Methylparaben	EP	4
Petrolatum, White	USP	4
Polyethylene Glycol	USP	4
Polysorbate 80	EP	3
Povidone	JP	5A
•Propylene Glycol	EP	2•4
Propyl Paraben	EP	4
Saccharin	USP	•6•4
Saccharin, Calcium	USP	•6•4
Saccharin, Sodium	USP	•6•4
Silicon Dioxide	JP	4
Silicon Dioxide, Collodial	JP	4
Sodium Chloride	EP	6
•Sodium Lauryl Sulfate	USP	2•4
Sodium Starch Glycolate	USP	5A
Starch, Corn	USP	6
Starch, Potato	EP	6
•Starch, Pregelatinized	JP	2•4
Starch, Rice	EP	4
Starch, Wheat	EP	6
Stearic Acid	EP	4
Sucrose	EP	3
Talc	EP	5A2
Titanium Dioxide	JP	5A2

Table 2. Status of Harmonization—General Chapters

Chapter Title	Coordinating Pharmacopeia	Harmonization Stage
Amino Acid Determination	USP	6
Bacterial Endotoxins	JP	7
Bulk Density and Tapped Density	EP	3
Degree of Color of Liquids; Clarity and Degree of Opalescence of Liquids	EP	3
Density of Solids	EP	3
Disintegration	USP	4
Dissolution	USP	4
Capillary Electrophoresis	EP	6
Polyacrylamide Gel Electrophoresis	EP	6
Extractable Volume of Parenterals	EP	6
Flowability (Powder Flow)	USP	4
Heavy Metals	USP	3
Inhalation	EP	3
Isoelectric Focusing	EP	6
Light Diffraction Measure of Particle Size	EP	3
Microbial Contamination	EP	3
Microbial Attributes	EP	3
Optical Microscopy	USP	4
Particle Size Distribution Estimation by Analytical Sieving	USP	4
Peptide Mapping	USP	6
Porosimetry by Mercury Intrusion	EP	3
Powder Fineness	USP	4
Protein Determination	USP	6
Residue on Ignition	JP	6
Specific Surface Area	EP	•4•4
Sterility Tests	EP	6
Tablet Friability	USP	3
Uniformity of Content/Mass	USP	4
X-Ray Diffraction—Solids	EP	3

•Harmonized Monographs and Chapters

HARMONIZED CHAPTERS

⟨85⟩ **Bacterial Endotoxins Test**—This chapter has been harmonized by PDG and published in the *European Pharmacopoeia* and in the *Japanese Pharmacopoeia*. Portions of the chapter that are not harmonized with the other two pharmacopeias are marked by the symbol ◆. Footnotes 1, 2, and 4 are in *USP* while they are not in *EP* or *JP*. These footnotes give additional information, such as the calculation of endotoxin limits for different classes of products (Footnote 4) or reference USP chapters (Footnote 2).

The USP Endotoxin Reference Standard is harmonized with the International Reference Standard for Endotoxin and the EP Endotoxin Reference Standard and indirectly harmonized with the JP Endotoxin Reference Standard that is indexed to the International Reference Standard. The result is that 1 USP Endotoxin Unit = 1 International Endotoxin Unit = 1 EP Endotoxin Unit.•4

GLOSSARY

Harmonized monograph or general chapter—Text that has reached Stage 5B and that has been countersigned by the three PDG pharmacopeias.

Total harmonization—A monograph or a general chapter that is identical in the three PDG pharmacopeias in terms of identical tests, test procedures, and acceptance criteria.

Harmonization by attributes—A monograph or a general chapter that contains a combination of harmonized and nonharmonized tests or sections.

Interchangeability—A test or a section of a monograph or a general chapter that is not the same among the PDG pharmacopeias, but the accept/reject decision is the same regardless of which one of the tests or sections of the PDG pharmacopeia is used.

Local or national divergence—A monograph or a general chapter in one of the PDG pharmacopeias contains specific attributes of local or national origin in addition to the PDG harmonized/nonharmonized attributes.

Nonharmonized attributes—Attributes that could not be agreed upon by the three PDG pharmacopeias due to regional differences, regulatory differences, nonavailability of reagents, etc.

APPENDIX

Example

Pharmacopeial Discussion Group

Sign-Off Document

Name: _____

Attributes	EP	JP	USP
1	+	+	+
2	+	+	–
3	+	+	+
4	+	+	+
5	+	+	+
6	+	+	+
7	+	–	+
8	+	+	+
9	+	+	+
10	+	–	+
11	+	+	+

Legend
+ will adopt and implement; – will not stipulate

Nonharmonized attributes

Reagents and reference materials
Each pharmacopeia will adapt the text to take account of local reference materials and reagent specifications.

Date:

Signatures:
European Pharmacopoeia Japanese Pharmacopoeia United States Pharmacopeia●1

Interim Revision Announcement

ERRATA

Following is a list of errata and corrections to *USP 26–NF 21*. The page number indicates where the item is found in *USP 26–NF 21*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in the next available annual edition or *Supplement*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
1	*General Notices and Requirements*	*Ingredients and Processes*	Line 7 of the 4th paragraph: Change "*Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩" to: *Pharmacy Compounding* ⟨795⟩
		Preservation, Packaging, Storage, and Labeling	Last line under *Pharmaceutical compounding* under *Labeling:* Change "*Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩" to: *Pharmacy Compounding* ⟨795⟩
93	*Aluminum Sulfate and Calcium Acetate Tablets for Topical Solution*	*Assay for calcium acetate*	Line 8: Change "1.742 mg" to: 1.762 mg
221	*Benzocaine, Butamben, and Tetracaine Hydrochloride Topical Aerosol*	*Assay*	Line 4 under *Assay preparation:* Change "125 mm of mercury" to: 600 mm of mercury
389	*Cefuroxime Axetil Tablets*	*Assay*	Line 4 under *Procedure:* Change "$(V/12{,}500N)(P_S W_S)(R_U/R_S)$," to: $(V/12{,}500N)(P_S W_S/100)(100-K)(R_U/R_S)$,
895	*Helium*	*Carbon monoxide*	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
1136	*Meclizine Hydrochloride Tablets*	*Dissolution*	Lines 2 and 3 under *Chromatographic system:* Change "4.6-mm × 4-cm precolumn" to: 4.6-mm × 25-cm precolumn
1159	*Mercaptopurine Tablets*	*Assay*	Line 20: Change "170.20" to: 170.19
1322	*Nitrous Oxide*	*Limit of nitric oxide*	Line 1: Change "550 ± 50 mL," to: 500 ± 50 mL,
		Carbon monoxide	Line 1: Change "1050 ± 50 mL," to: 1000 ± 50 mL,
		Halogens	Line 1: Change "1050 ± 50 mL," to: 1000 ± 50 mL,
		Carbon dioxide	Line 1: Change "1050 ± 50 mL," to: 1000 ± 50 mL,
1372	*Oxygen*	*Carbon dioxide*	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
		Carbon monoxide	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
1373	*Oxygen 93 Percent*	*Carbon dioxide*	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
		Carbon monoxide	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
1433	*Perflubron*	*Specific gravity*	Line 1: Change "1.916 and 1.919." to: 1.922 and 1.925.
1720	*Sufentanil Citrate Injection*	*Definition*	Line 5: Change "sufentanil ($C_{22}H_{30}N_2O_2S$), as the citrate." to: sufentanil citrate ($C_{22}H_{30}N_2O_2S \cdot C_6H_8O_7$).
1932	*Vinorelbine Tartrate*	*Assay*	Line 2: Change "40.0 mL of acetic acid." to: 40.0 mL of glacial acetic acid.
2092	⟨563⟩ *Identification of Articles of Botanical Origin*		This new chapter should display ***Add the following:*** before the title, and ▲ at its beginning and end.
2125	⟨616⟩ *Bulk Density and Tapped Density*	*Bulk Density*	Line 14 under *Procedure* in *Method I—Measurement in a Graduated Cylinder*: Change "$(M)/(V_f)$." to: $(M)/(V_o)$.
		Tapped Density	Line 28 under *Method I*: Change "$(M)/(V_o)$." to: $(M)/(V_f)$.
2189	⟨788⟩ *Particulate Matter in Injections*	*Microscopic Particle Count Test*	Table 2 under *Interpretation*: Microscopic Method Particle Count is missing 2 column headers. Change to:

Table 2. Microscopic Method Particle Count

	≥10 µm	≥25 µm
Small-Volume Injections	3000	300 per container
Large-Volume Injections	12	2 per mL

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Page	Title	Section	Description
2471	*Reagents Specifications*	*4-(Butylamino)benzoic Acid*	Line 2: Change footnote "[104]" to: [96]
2598	*Reference Tables*	*Alcoholometric Table*	Adjust column widths and headers, thereby correcting alignment of column heads. Reprinted on the following pages for clarity.
2686	*Acetyltributyl Citrate*	*Assay*	Lines 1–11 under *Chromatographic system*, ending with "about 2.3 mL per minute." Revert to the official text as published in *NF 20,* page 2503. Reprinted on the following pages for clarity. Line 2 under *Procedure:* Change "about 1.0 µL" to: 1 µL; Line 7 under *Procedure:* Change "100*A*/*B*," to: 100(*A*/*B*),
2687	*Acetyltriethyl Citrate*	*Assay*	Lines 1–11 under *Chromatographic system*, ending with "about 2.3 mL per minute." Revert to the official text as published in *NF 20,* page 2504. Reprinted on the following pages for clarity. Line 2 under *Procedure:* Change "about 1.0 µL" to: 1 µL; Line 7 under *Procedure:* Change "100*A*/*B*," to: 100(*A*/*B*),
2800	*Nitrogen*	*Carbon monoxide*	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
2801	*Nitrogen 97 Percent*	*Carbon dioxide*	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
		Carbon monoxide	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
		Sulfur dioxide	Line 1: Change "1050 ± 50 mL" to: 1000 ± 50 mL
		Limit of nitric oxide and nitrogen dioxide	Line 1: Change "550 ± 50 mL" to: 500 ± 50 mL
2810	*Polyethylene Glycol*	*Limit of ethylene glycol and diethylene glycol*	Revert to the official text as published on page 2920 of the *Second Supplement* to *NF 20*, reprinted on the following page for clarity.
2851	*Tributyl Citrate*	*Assay*	Lines 1–11 under *Chromatographic system*, ending with "about 2.3 mL per minute." Revert to the official text as published in *NF 20,* page 2635. Reprinted on the following pages for clarity. Line 1 under *Procedure:* reinsert NOTE—Use peak areas where peak responses are indicated.; Line 1 under *Procedure:* Change "about 1.0 µL" to: 1 µL; Line 7 under *Procedure:* Change "100*A*/*B*," to: 100(*A*/*B*),
2852	*Triethyl Citrate*	*Assay*	Lines 1–11 under *Chromatographic system*, ending with "about 2.3 mL per minute." Revert to the official text as published in *NF 20,* page 2635. Reprinted on the following pages for clarity. Line 1 under *Procedure:* reinsert NOTE—Use peak areas where peak responses are indicated.; Line 1 under *Procedure:* Change "a volume (about 1.0 µL)" to: 1 µL
Supplement 1			
2942	*Amoxicillin Tablets for Oral Suspension*	*Definition*	Line 3: Change "$C_{12}H_{15}N_3O_2S$" to: $C_{16}H_{19}N_3O_5S$
		Dissolution	Line 2 of paragraph after *Time:* Change "$C_{12}H_{15}N_3O_2S$" to: $C_{16}H_{19}N_3O_5S$; Line 2 under *Tolerances:* Change "$C_{12}H_{15}N_3O_2S$" to: $C_{16}H_{19}N_3O_5S$
		Assay	Line 3 under *Procedure:* Change "$C_{12}H_{15}N_3O_2S$" to: $C_{16}H_{19}N_3O_5S$
2968	*Hydrochlorothiazide Tablets*	*Related compounds*	Line 5 under *Procedure:* Change "in the portion of Hydrochlorothiazide" to: in the portion of Tablets

Interim Revision Announcement

ALCOHOLOMETRIC TABLE

Based on data appearing in the National Bureau of Standards Bulletin, vol. 9, pp. 424–425 (publication of the National Institute of Standards and Technology).

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Percentage of C_2H_5OH		Specific gravity in air		Percentage of C_2H_5OH		Specific gravity in air	
By volume at 15.56°C	By weight	$at\ \frac{25^\circ}{25^\circ}$	$at\ \frac{15.56^\circ}{15.56^\circ}$	By weight	By volume at 15.56°C	$at\ \frac{25^\circ}{25^\circ}$	$at\ \frac{15.56^\circ}{15.56^\circ}$
0	0.00	1.0000	1.0000	0	0.00	1.0000	1.0000
1	0.80	0.9985	0.9985	1	1.26	0.9981	0.9981
2	1.59	0.9970	0.9970	2	2.51	0.9963	0.9963
3	2.39	0.9956	0.9956	3	3.76	0.9945	0.9945
4	3.19	0.9941	0.9942	4	5.00	0.9927	0.9928
5	4.00	0.9927	0.9928	5	6.24	0.9911	0.9912
6	4.80	0.9914	0.9915	6	7.48	0.9894	0.9896
7	5.61	0.9901	0.9902	7	8.71	0.9879	0.9881
8	6.42	0.9888	0.9890	8	9.94	0.9863	0.9867
9	7.23	0.9875	0.9878	9	11.17	0.9848	0.9852
10	8.05	0.9862	0.9866	10	12.39	0.9833	0.9839
11	8.86	0.9850	0.9854	11	13.61	0.9818	0.9825
12	9.68	0.9838	0.9843	12	14.83	0.9804	0.9812
13	10.50	0.9826	0.9832	13	16.05	0.9789	0.9799
14	11.32	0.9814	0.9821	14	17.26	0.9776	0.9787
15	12.14	0.9802	0.9810	15	18.47	0.9762	0.9774
16	12.96	0.9790	0.9800	16	19.68	0.9748	0.9763
17	13.79	0.9778	0.9789	17	20.88	0.9734	0.9751
18	14.61	0.9767	0.9779	18	22.08	0.9720	0.9738
19	15.44	0.9756	0.9769	19	23.28	0.9706	0.9726
20	16.27	0.9744	0.9759	20	24.47	0.9692	0.9714
21	17.10	0.9733	0.9749	21	25.66	0.9677	0.9701
22	17.93	0.9721	0.9739	22	26.85	0.9663	0.9688
23	18.77	0.9710	0.9729	23	28.03	0.9648	0.9675
24	19.60	0.9698	0.9719	24	29.21	0.9633	0.9662
25	20.44	0.9685	0.9708	25	30.39	0.9617	0.9648
26	21.29	0.9673	0.9697	26	31.56	0.9601	0.9653
27	22.13	0.9661	0.9687	27	32.72	0.9585	0.9620
28	22.97	0.9648	0.9676	28	33.88	0.9568	0.9605
29	23.82	0.9635	0.9664	29	35.03	0.9551	0.9590
30	24.67	0.9622	0.9653	30	36.18	0.9534	0.9574
31	25.52	0.9609	0.9641	31	37.32	0.9516	0.9558
32	26.38	0.9595	0.9629	32	38.46	0.9498	0.9541
33	27.24	0.9581	0.9617	33	39.59	0.9480	0.9524
34	28.10	0.9567	0.9604	34	40.72	0.9461	0.9506
35	28.97	0.9552	0.9590	35	41.83	0.9442	0.9488
36	29.84	0.9537	0.9576	36	42.94	0.9422	0.9470
37	30.72	0.9521	0.9562	37	44.05	0.9402	0.9451
38	31.60	0.9506	0.9548	38	45.15	0.9382	0.9432
39	32.48	0.9489	0.9533	39	46.24	0.9362	0.9412
40	33.36	0.9473	0.9517	40	47.33	0.9341	0.9392
41	34.25	0.9456	0.9501	41	48.41	0.9320	0.9372
42	35.15	0.9439	0.9485	42	49.48	0.9299	0.9352
43	36.05	0.9421	0.9469	43	50.55	0.9278	0.9331
44	36.96	0.9403	0.9452	44	51.61	0.9256	0.9310
45	37.87	0.9385	0.9434	45	52.66	0.9235	0.9289
46	38.78	0.9366	0.9417	46	53.71	0.9213	0.9268
47	39.70	0.9348	0.9399	47	54.75	0.9191	0.9246
48	40.62	0.9328	0.9380	48	55.78	0.9169	0.9225
49	41.55	0.9309	0.9361	49	56.81	0.9147	0.9203
50	42.49	0.9289	0.9342	50	57.83	0.9124	0.9181
51	43.43	0.9269	0.9322	51	58.84	0.9102	0.9159
52	44.37	0.9248	0.9302	52	59.85	0.9079	0.9137
53	45.33	0.9228	0.9282	53	60.85	0.9056	0.9114

(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
54	46.28	0.9207	0.9262	54	61.85	0.9033	0.9092
55	47.25	0.9185	0.9241	55	62.84	0.9010	0.9069
56	48.21	0.9164	0.9220	56	63.82	0.8987	0.9046
57	49.19	0.9142	0.9199	57	64.80	0.8964	0.9024
58	50.17	0.9120	0.9177	58	65.77	0.8941	0.9001
59	51.15	0.9098	0.9155	59	66.73	0.8918	0.8978
60	52.15	0.9076	0.9133	60	67.79	0.8895	0.8955
61	53.15	0.9053	0.9111	61	68.64	0.8871	0.8932
62	54.15	0.9030	0.9088	62	69.59	0.8848	0.8909
63	55.17	0.9006	0.9065	63	70.52	0.8824	0.8886
64	56.18	0.8983	0.9042	64	71.46	0.8801	0.8862
65	57.21	0.8959	0.9019	65	72.38	0.8777	0.8839
66	58.24	0.8936	0.8995	66	73.30	0.8753	0.8815
67	59.28	0.8911	0.8972	67	74.21	0.8729	0.8792
68	60.33	0.8887	0.8948	68	75.12	0.8706	0.8768
69	61.38	0.8862	0.8923	69	76.02	0.8682	0.8745
70	62.44	0.8837	0.8899	70	76.91	0.8658	0.8721
71	63.51	0.8812	0.8874	71	77.79	0.8634	0.8697
72	64.59	0.8787	0.8848	72	78.67	0.8609	0.8673
73	65.67	0.8761	0.8823	73	79.54	0.8585	0.8649
74	66.77	0.8735	0.8797	74	80.41	0.8561	0.8625
75	67.87	0.8709	0.8771	75	81.27	0.8537	0.8601
76	68.98	0.8682	0.8745	76	82.12	0.8512	0.8576
77	70.10	0.8655	0.8718	77	82.97	0.8488	0.8552
78	71.23	0.8628	0.8691	78	83.81	0.8463	0.8528
79	72.38	0.8600	0.8664	79	84.64	0.8439	0.8503
80	73.53	0.8572	0.8636	80	85.46	0.8414	0.8479
81	74.69	0.8544	0.8608	81	86.28	0.8389	0.8454
82	75.86	0.8516	0.8580	82	87.08	0.8364	0.8429
83	77.04	0.8487	0.8551	83	87.89	0.8339	0.8404
84	78.23	0.8458	0.8522	84	88.68	0.8314	0.8379
85	79.44	0.8428	0.8493	85	89.46	0.8288	0.8354
86	80.66	0.8397	0.8462	86	90.24	0.8263	0.8328
87	81.90	0.8367	0.8432	87	91.01	0.8237	0.8303
88	83.14	0.8335	0.8401	88	91.77	0.8211	0.8276
89	84.41	0.8303	0.8369	89	92.52	0.8184	0.8250
90	85.69	0.8271	0.8336	90	93.25	0.8158	0.8224
91	86.99	0.8237	0.8303	91	93.98	0.8131	0.8197
92	88.31	0.8202	0.8268	92	94.70	0.8104	0.8170
93	89.65	0.8167	0.8233	93	95.41	0.8076	0.8142
94	91.03	0.8130	0.8196	94	96.10	0.8048	0.8114
95	92.42	0.8092	0.8158	95	96.79	0.8020	0.8086
96	93.85	0.8053	0.8118	96	97.46	0.7992	0.8057
97	95.32	0.8011	0.8077	97	98.12	0.7962	0.8028
98	96.82	0.7968	0.8033	98	98.76	0.7932	0.7998
99	98.38	0.7921	0.7986	99	99.39	0.7902	0.7967
100	100.00	0.7871	0.7936	100	100.00	0.7871	0.7936

Acetyltributyl Citrate

Assay—

Chromatographic system (see *Chromatography* 621)—The gas chromatograph is equipped with an on-column, temperature-programmable injector, a flame-ionization detector maintained at about 275°, and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed to be maintained at about 80° for 0.5 minute, then to increase to about 220° at a rate of 20° per minute, and to hold at about 220° for 10 minutes. The injection port temperature is programmed to be maintained at about 85° for 0.5 minute, then to increase to about 225° at a rate of 20° per minute, and to hold at about 225° for 10 minutes. Heilum is used as the carrier gas at a flow rate of about 2.3 mL per minutes. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for tributyl citrate and 1.0 for acetyltributyl citrate; the resolution, *R*, between tributyl citrate and acetyltributyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the tributyl citrate and acetyltributyl citrate peaks, based on area percent calculation.

Acetyltriethyl Citrate

Assay—

Chromatographic system (see *Chromatography* 621)—The gas chromatograph is equipped with an on-column, temperature-programmable injector, a flame-ionization detector maintained at about 275°, and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed to be maintained at about 80° for 0.5 minute, then to increase to about 220° at a rate of 20° per minute, and to hold at about 220° for 10 minutes. The injection port temperature is programmed to be maintained at about 85° for 0.5 minute, then to increase to about 225° at a rate of 20° per minute, and to hold at about 225° for 10 minutes. Helium is used as the carrier gas at a flow rate of about 2.3

mL per minutes. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for triethyl citrate and 1.0 for acetyltriethyl citrate; the resolution, *R*, between triethyl citrate and acetyltriethyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the triethyl citrate and acetyltriethyl citrate peaks, based on area percent calculation.

Polyethylene Glycol

Limit of ethylene glycol and diethylene glycol (for Polyethylene Glycol having a nominal molecular weight less than 450)—

Standard preparation—Prepare an aqueous solution containing 500 µg each of ethylene glycol and of diethylene glycol per mL.

Test preparation—Transfer about 4 g of Polyethylene Glycol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* 621)—The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 1.5-m stainless steel column packed with 12% G13 on support S1NS. The carrier gas is nitrogen or another suitable inert gas, flowing at a rate of 50 mL per minute. The column temperature is maintained at about 140°, the injection port temperature is maintained at about 250°, and the flame-ionization detector temperature is maintained at 280°.

Procedure—Inject a volume (about 2.0 µL) of the *Standard preparation* into the chromatograph, and record the chromatogram, adjusting the operational conditions to obtain peaks not less than 10 cm in height. Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as P_1 and P_2, respectively. Inject a volume (about 2.0 µL) of the *Test preparation* into the chromatograph, and record the chromatogram under the same conditions as those employed for the *Standard preparation*. Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as $p_1$and p_2, respectively. Calculate the percentage of ethylene glycol in the portion of Polyethylene Glycol taken by the formula:

$$(C_1 p_1)/(P_1 W),$$

in which C_1 is the concentration, in µg per mL, of ethylene glycol in the *Standard preparation;* and W is the weight, in mg, of Polyethylene Glycol taken. Calculate the percentage of diethylene glycol in the portion of Polyethylene Glycol taken by the formula:

$$(C_2 p_2)/(P_2 W),$$

in which C_2 is the concentration, in µg per mL, of diethylene glycol in the *Standard preparation:* not more than 0.25% of the sum of ethylene glycol and diethylene glycol is found.

Tributyl Citrate

Assay—

Chromatographic system (see *Chromatography* 621)—The gas chromatograph is equipped with an on-column, temperature-programmable injector, a flame-ionization detector maintained at about 275°, and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed to be maintained at about 80° for 0.5 minute, then to increase to about 220° at a rate of 20° per minute, and to hold at about 220° for 10 minutes. The injector port temperature is programmed to be maintained at about 85° for 0.5 minute, then to increase to about 225° at a rate of 20° per minute, and to hold at about 225° for 10 minutes. Helium is used as the carrier gas at a flow rate of about 2.3 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for tributyl citrate and 1.0 for acetyltributyl citrate; the resolution, *R*, between tributyl citrate and acetyltributyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the tributyl citrate and acetyltributyl citrate peaks, based on area percent calculation.

Triethyl Citrate

Assay—

Chromatographic system (see *Chromatography* 621)—The gas chromatograph is equipped with an on-column, temperature-programmable injector, a flame-ionization detector maintained at about 275°, and a 0.32-mm × 30-m column bonded with a 0.5-µm layer of phase G42. The column temperature is programmed to be maintained at about 80° for 0.5 minute, then to increase to about 220° at a rate of 20° per minute, and to hold at about 220° for 10 minutes. The injector port temperature is programmed to be maintained at about 85° for 0.5 minute, then to increase to about 225° at a rate of 20° per minute, and to hold at about 225° for 10 minutes. Helium is used as the carrier gas at a flow rate of about 2.3 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for triethyl citrate and 1.0 for acetyltriethyl citrate; the resolution, *R*, between triethyl citrate and acetyltriethyl citrate is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0% determined from both the triethyl citrate and acetyltriethyl citrate peaks, based on area percent calculation.

IN-PROCESS REVISION

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

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

BRIEFING

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

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

•new text•

if slated for an *Interim Revision Announcement to USP 26–NF 21* (*IRA*), thus:

▲new text▲*USP27*

if slated for *USP 27–NF 22*, and thus:

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, and ■2S (*USP 27*) indicates that the proposed revision is slated for the *Second Supplement to USP 27*, and ▲*USP27* and ▲*NF22* indicate that the revisions are proposed for *USP 27* and *NF 22*, respectively.

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

In-Process Revision

In-Process Revision

BRIEFING

General Notices and Requirements, *USP 26* page 3, page 2938 of the *First Supplement*, and page 1757 of *PF* 28(6) [Nov.–Dec. 2002]. The proposed revisions in the section *Significant Figures and Tolerances* are intended to clarify and provide consistency regarding the use of rounded or unrounded numbers in the calculation of analytical results. The term "reportable result" is also introduced and discussed.

In addition, it is proposed to add a subsection on *Residual Solvents* in the section *Foreign Substances and Impurities* under *Tests and Assays*, to provide consistency with revisions to general chapters *Organic Volatile Impurities* ⟨467⟩ and *Impurities in Official Articles* ⟨1086⟩. (See briefing under *Organic Volatile Impurities* ⟨467⟩, appearing elsewhere in this number of *PF*.)

Several favorable comments were received on the proposal that appeared in *PF* 28(5) to revise the section on *Test Results*, *Statistics*, *and Standards* under *Tests and Assays* to allow the use of the average of results of the *Content Uniformity* determinations to be used as the *Assay* value. This provision requires that the determination of *Content Uniformity* must be performed using the same method specified in the *Assay* in the individual monograph. Other comments raised several issues:

1. There was a question as to whether the "same" method meant the "identical" method specified in the *Assay*. It is recognized in the general chapter *Uniformity of Dosage Units* ⟨905⟩, that in performing the test for *Content Uniformity* in order to assay individual dosage units, different volumes of diluent may be required. Other than that, the procedure is identical. Therefore, it is proposed to change the words "same method" to "same procedure" specified in the *Assay*.
2. One comment noted that the proposal stated that the average of the *Content Uniformity* determinations "may be used" as the *Assay* value. There was a question as to how to resolve any dispute if differences occur between results of the average of the *Content Uniformity* determinations and results in the *Assay*. The Committee agreed that in view of the fact that the *Content Uniformity* determinations are made using the same procedure as is specified in the *Assay*, no significant differences are likely. This option allows flexibility in laboratory operations.
3. A question was raised as to which of the possible *Content Uniformity* determinations should be averaged, that is, the initial 10 units, the next 20 units, or the total of 30 units. It is proposed to state that "the average of *all* of the individual *Content Uniformity* determination is used as the *Assay* value."

Finally, in the section *Preservative*, *Packaging*, *Storage*, *and Labeling*, it is proposed to add *Repackaging Instructions* to provide information, supporting the current statement in 21 CFR 201 · 100 and to clarify the repackaging process.

(BST: W. Paul; PSD: C. Okeke; PA2: W. Paul; PA7a: W. Wright) RTS—39444-1; 39905-1; 39967; 39711-1

Change to read:

"OFFICIAL" AND "OFFICIAL ARTICLES"

The word "official," as used in this Pharmacopeia or with reference hereto, is synonymous with "Pharmacopeial," with "USP," and with "compendial."

The designation "USP" in conjunction with the official title or elsewhere on the label of an article ~~means that the article~~

▲indicates that a monograph is included in the *USP* and that

the article▲*USP27*
purports to comply with

▲all applicable▲*USP27*
USP standards.
~~Any language modifying or limiting this representation shall be accompanied by a statement that the article is "not USP".such specific~~

▲The▲*USP27*
designation

▲"USP"▲*USP27*
on the label

▲may not and▲*USP27*
does not constitute a representation, endorsement, or incorporation by the manufacturer's labeling of the informational material contained in the USP monograph, nor does it constitute assurance by USP that the article is known to comply with USP standards. An article may only purport to comply with a USP standard

▲or other requirements▲*USP27*
when the article is recognized in the *USP*. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, whether or not the added designation "USP" is used. Names considered to be synonyms of the official titles may not be used for official titles.

Although both compendia, the *United States Pharmacopeia* and the *National Formulary*, currently are published under one cover, they remain separate compendia. The designation *USP–NF* or similar combination may be used on the label of an article, provided the label also bears a statement such as, "Meets *NF* standards as published by the USP," indicating the particular compendium to which the article purports to apply.

Where an article differs from the standards of strength, quality, and purity, as determined by the application of the assays and tests set forth for it in the Pharmacopeia, its difference shall be plainly stated on its label. Where an article fails to comply in identity with the identity prescribed in the *USP*, or contains an added substance that interferes with the prescribed assays and tests, such article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in the Pharmacopeia.

Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for use as drugs, as nutritional or dietary supplements, or as medical devices and when bought, sold, or dispensed for these purposes or when labeled as conforming to this Pharmacopeia.

An article is deemed to be recognized in this Pharmacopeia when a monograph for the article is published in it, including its supplements, addenda, or other interim revisions, and an official date is generally or specifically assigned to it.

The following terminology is used for distinguishing the articles for which monographs are provided: an *official substance* is an active drug entity, a recognized nutrient, a dietary supplement ingredient, or a pharmaceutic ingredient (see also *NF 21*) or a component of a finished device for which the monograph title includes no indication of the nature of the finished form; an *official preparation* is a *drug product*, a *nutritional supplement*, a *dietary supplement* or a *finished device*. It is the finished or partially finished (e.g., as in the case of a sterile solid to be constituted into a solution for administration) preparation or product of one or more

official substances formulated for use on or for the patient or consumer; an *article* is an item for which a monograph is provided, whether an official substance or an official preparation.

▲*Designating Conformance with Official Standards*—When the letters "USP" or "NF" or "USP–NF" are utilized on the label of an article to indicate compliance with compendial standards, the letters shall appear in conjunction with the official title of the article or when appropriate, with the ingredients contained therein. The letters are not to be enclosed in any symbol such as a circle, square, etc., and must appear in block capital letters.

If a dietary supplement purports to be or is represented as an official product and such claim is determined by USP not to be made in good faith, it is the policy of the USP to seek appropriate legal redress.▲*USP27*

Products Not Marketed in the United States—Interest in the USP outside the United States has always existed. From time to time, monographs may be adopted for articles not legally marketed in the United States as a service to authorities in other countries where USP standards are recognized and applied. Appearance of any such monograph does not grant any marketing rights whatsoever, and the status of the article in the United States must be checked with the U.S. Food and Drug Administration in the event of any question.

Nutritional and Other Dietary Supplements—The designation of an official preparation containing one or more recognized nutrients or dietary supplement ingredients as "USP" or the use of the designation "USP" in conjunction with the title of such nutritional or dietary supplement preparation may be made only if the preparation meets

▲all▲*USP27*
the applicable requirements contained in the individual monograph and general chapters.

▲Any language modifying or limiting this representation shall be accompanied by a statement indicating that the article is "not USP", and indicating how the article differs from the standards of strength, quality, or purity as determined by the application of the tests and assays set forth in the compendia.▲*USP27*
Any additional ingredient in such article that is not recognized in the Pharmacopeia and for which nutritional value is claimed shall not be represented nor imply that such ingredient is of USP quality or recognized by USP. If a preparation does not comply with

▲all▲*USP27*
applicable requirements but contains nutrients or dietary supplement ingredients that are recognized in the *USP*, the article may not designate the individual nutrients or ingredients as complying with USP standards or being of USP quality without designating on the label that the article itself does not comply with USP standards.

Change to read:

SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures—The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see *Titrimetry* ⟨541⟩).

Tolerances—The limits specified in the monographs for Pharmacopeial articles are established with a view to the use of these articles as drugs, nutritional or dietary supplements, or devices, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

A dosage form shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label. ~~Where the content of an ingredient is known to decrease with time, an amount in excess of that declared on the label may be introduced into the dosage form at the time of manufacture to assure compliance with the content requirements of the monograph throughout the expiration period.~~

■■2S (*USP26*)
The tolerances and limits stated in the definitions in the monographs for Pharmacopeial articles allow ~~for such overages and~~

■■2S (*USP26*)
for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. Where the minimum amount of a substance present in a nutritional or dietary supplement is required to be higher than the lower tolerance limit allowed for in the monograph because of applicable legal requirements, then the upper tolerance limit contained in the monograph shall be increased by a corresponding amount.

The specified tolerances are based upon such attributes of quality as might be expected to characterize an article produced from suitable raw materials under recognized principles of good manufacturing practice.

The existence of compendial limits or tolerances does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" the Pharmacopeial quality. Similarly, the fact that an article has been prepared to closer tolerances than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the Pharmacopeial requirements.

Interpretation of Requirements—Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated limits to determine whether there is conformance with compendial assay or test requirements. The observed or calculated values usually will contain more significant figures than there are in the stated limit, and ~~an observed or calculated~~

■a reportable■1S (*USP27*)

In-Process Revision

result is to be rounded off to the number of places that is in agreement with the limit expression by the following procedure. ~~[NOTE—Limits, which are fixed numbers, are not rounded off.]~~

■Intermediate calculations (e.g., slope for linearity in *Validation of Compendial Methods* ⟨1225⟩) may be rounded for reporting purposes, but the original value (not rounded) should be used for any additional required calculations. Rounding off should not be done until the final calculations for the reportable value have been completed. [NOTE—Limits, which are fixed numbers, are not rounded off.]

A reportable value is often a summary value for several individual determinations. It is the end result of a completed measurement method, as documented. It is the value compared with the acceptance criterion. In most cases, the reportable value is used as documentation for internal or external users.■1S (*USP27*)

When rounding off is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is greater than 5, it is eliminated and the preceding digit is increased by one. If this digit equals 5, the 5 is eliminated and the preceding digit is increased by one.

Illustration of Rounding Numerical Values for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit ≥98.0%	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit ≤101.5%	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes
Limit test ≤0.02%	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤3 ppm	0.00035%	0.0004%	No
	0.00025%	0.0003%	Yes
	0.00028%	0.0003%	Yes

Change to read:

TESTS AND ASSAYS

Apparatus—A specification for a definite size or type of container or apparatus in a test or assay is given solely as a recommendation. Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed. (See also *Thermometers* ⟨21⟩, *Volumetric Apparatus* ⟨31⟩, and *Weights and Balances* ⟨41⟩.) Where low-actinic or light-resistant containers are specified, clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

Where an instrument for physical measurement, such as a spectrophotometer, is specified in a test or assay by its distinctive name, another instrument of equivalent or greater sensitivity and accuracy may be used. In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used, solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure.

Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification. Items capable of equal or better performance may be used if these characteristics have been validated.

Where the use of a centrifuge is indicated, unless otherwise specified, the directions are predicated upon the use of apparatus having an effective radius of about 20 cm (8 inches) and driven at a speed sufficient to clarify the supernatant layer within 15 minutes.

Unless otherwise specified, for chromatographic tubes and columns the diameter specified refers to internal diameter (ID); for other types of tubes and tubing the diameter specified refers to outside diameter (OD).

Steam Bath—Where the use of a steam bath is directed, exposure to actively flowing steam or to another form of regulated heat, corresponding in temperature to that of flowing steam, may be used.

Water Bath—Where the use of a water bath is directed without qualification with respect to temperature, a bath of vigorously boiling water is intended.

Foreign Substances and Impurities—Tests for the presence of foreign substances and impurities are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* ⟨1086⟩).

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the source of material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.

Other Impurities—Official substances may be obtained from more than one process, and thus may contain impurities not considered during preparation of monograph assays or tests. Wherever a monograph includes a chromatographic assay or purity test based on chromatography, other than a test for ~~organic volatile impurities,~~

■residual solvents■1S (*USP27*)

and that monograph does not detect such an impurity, solvents excepted, the impurity shall have its amount and identity, where both are known, stated under the heading *Other Impurity*(*ies*) by the labeling (certificate of analysis) of the official substance.

The presence of any unlabeled impurity in an official substance is a variance from the standard if the content is 0.1% or greater. Tests suitable for detection and quantitating unlabeled impurities, when present as the result of process change or other identifiable, consistent occurrence, shall be submitted to the USP for inclusion in the individual monograph. Otherwise, the impurity shall be identified, preferably by name, and the amount listed under the heading *Other Impurity*(*ies*) in the labeling (certificate of analysis) of the official substance. The sum of all *Other Impurities* combined with the monograph-detected impurities does not exceed 2.0% (see *Ordinary Impurities* ⟨466⟩), unless otherwise stated in the monograph.

Categories of drug substances excluded from *Other Impurities* requirements are fermentation products and semi-synthetics derived therefrom, radiopharmaceuticals, biologics, biotechnology-derived products, peptides, herbals, and crude products of animal or plant origin. Any substance known to be toxic must not be listed under *Other Impurities*.

■**Residual Solvents**—The requirements are stated in *Organic Volatile Impurities* ⟨467⟩ together with information in *Impurities in Official Articles* ⟨1086⟩. Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in *Organic Volatile Impurities* ⟨467⟩, using the general methods presented therein or other suitable methods.■1S (*USP27*)

Procedures—Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing *process validation* studies and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not less than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy. To minimize environmental impact or contact with hazardous materials, apparatus and chemicals specified in Pharmacopeial procedures also may be proportionally changed.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not fewer than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.

Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not less than a given number, usually 20, of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.

Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the *Assay* procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on drying*, or *Water*, or *Loss on ignition*, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for *Loss on drying* or *Water*, the expression "previously dried" without qualification signifies that the substance is to be dried as directed under *Loss on drying* or *Water* (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter *USP Reference Standards* ⟨11⟩, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within 10% of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under *Volumetric Apparatus* ⟨31⟩, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under *Volumetric Apparatus* ⟨31⟩ , may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as "25.0 mL" and "25.0 mg," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under *Volumetric Apparatus* ⟨31⟩ or under *Weights and Balances* ⟨41⟩.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also *Use of Reference Standards* under *Spectrophotometry and Light-Scattering* ⟨851⟩.

Blank Determination—Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

Desiccator—The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution—Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see *Volumetric Apparatus* ⟨31⟩).

Drying to Constant Weight—The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration—Where it is directed to "filter," without further qualification, the intent is that the liquid be filtered through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests—The Pharmacopeial tests headed *Identification* are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight—The specification "ignite to constant weight" means that the ignition shall be continued, at 800 ± 25° unless otherwise indicated, until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators—Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL, or 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms—Logarithms used in the assays are to the base 10.

Microbial Strains—Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible—This term indicates a quantity not exceeding 0.50 mg.

Odor—Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article (for packages containing not more than 25 g) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about 100-mL capacity. An odor designation is descriptive only and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements—The term "mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions—Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with *Purified Water*.

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid is to be diluted with, or 1 part *by weight* of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts *by volume*.

An expression such as "(20:5:2)" means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under *Volumetric Solutions* in the section *Reagents, Indicators, and Solutions*, and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity—Unless otherwise stated, the specific gravity basis is 25°/25°, i.e., the ratio of the weight of a substance in air at 25° to the weight of an equal volume of water at the same temperature.

Temperatures—Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at 25°. Where moderate heat is specified, any temperature not higher than 45° (113°F) is indicated. See *Storage Temperature* under *Preservation, Packaging, Storage, and Labeling* for other definitions.

Time Limit—In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum—The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water—Where water is called for in tests and assays, Purified Water is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide–free water," see the introduction to the section *Reagents, Indicators, and Solutions*. For *High-purity Water* see *Containers* ⟨661⟩.

Water and Loss on Drying—Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading *Water*. Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading *Loss on drying*. However, *Loss on*

drying is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Test Results, Statistics, and Standards—Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply.

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for *Dissolution* and *Uniformity of dosage units*, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.

▲Where the *Content Uniformity* determinations have been made using the same ~~method~~ procedure specified in the *Assay*, the average of all of the individual *Content Uniformity* determinations may be used as the *Assay* value.▲*USP27*

Description—Information on the "description" pertaining to an article, which is relatively general in nature, is provided in the reference table *Description and Relative Solubility of USP and NF Articles* in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility—The statements concerning solubilities given in the reference table *Description and Relative Solubility of USP and NF Articles* for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	Greater than or equal to 10,000

Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

▲**Interchangeable Methods**—Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method from one of these pharmacopeias, it should comply with the requirements of the *United States Pharmacopeia*. However, where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.▲*USP26*

Change to read:

PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers—The *container* is that which holds the article and is or may be in direct contact with the article. The *immediate container* is that which is in direct contact with the article at all times. The *closure* is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

~~*Tamper-Resistant*~~

■*Tamper-Evident*■2S (*USP26*)

Packaging—The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the ~~tamper-resistant~~

■tamper-evident■2S (*USP26*)
packaging and labeling requirements of the FDA where applicable.

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Preferably, the immediate container and/or the outer container or protective packaging utilized by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-Resistant Container (see *Light Transmission* under *Containers* ⟨661⟩)—A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to ''protect from light'' in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-Closed Container—A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container—A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE—Where packaging and storage in a *tight container* or a *well-closed container* is specified in the individual monograph, the container utilized for an article when dispensed on prescription meets the requirements under *Containers—Permeation* ⟨671⟩.

Hermetic Container—A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-Unit Container—A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-Dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-Dose Container—A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Unit-of-Use Container—A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

Multiple-Unit Container—A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-Dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

Storage Temperature and Humidity—Specific directions are stated in some monographs with respect to the temperatures and humidity at which Pharmacopeial articles shall be stored and distributed (including the shipment of articles to the consumer) when stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply (see also *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩.) The conditions are defined by the following terms.

Freezer—A place in which the temperature is maintained thermostatically between –25° and –10° (–13° and 14 °F).

Cold—Any temperature not exceeding 8° (46 °F). A *refrigerator* is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46 °F).

Cool—Any temperature between 8° and 15° (46° and 59 °F). An article for which storage in a *cool place* is directed may, alternatively, be stored and distributed in a *refrigerator*, unless otherwise specified by the individual monograph.

Room Temperature—The temperature prevailing in a working area.

Controlled Room Temperature—A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77 °F); that results in a mean kinetic temperature calculated to be not more than 25°; and that allows for excursions between 15° and 30° (59° and 86 °F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40° are permitted as long as they do not exceed 24 hours. Spikes above 40° may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩.)

An article for which storage at *Controlled room temperature* is directed may, alternatively, be stored and distributed in a *cool place*, unless otherwise specified in the individual monograph or on the label.

Warm—Any temperature between 30° and 40° (86° and 104 °F).

Excessive Heat—Any temperature above 40° (104 °F).

Protection from Freezing—Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Dry Place—The term "dry place" denotes a place that does not exceed 40% average relative humidity at *Controlled Room Temperature* or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value is 40% relative humidity.

Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered a dry place.

Storage under Nonspecific Conditions—~~For articles, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution include protection from moisture, freezing, and excessive heat.~~

▲Where no specific directions or limitations are provided in the packaging and storage section of individual monographs or in the article's labeling, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Articles shall be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Active pharmaceutical ingredients are exempt from this requirement.▲*USP27*

■**Repackaging Instructions**—Except where a drug product is packaged in a container intended to be dispensed directly to the patient, such as a unit-of-use or unit-dose container, the labeling shall contain directions specifying the types of containers suitable for repackaging the drug product so as to maintain its identity, strength, quality, and purity. Such directions shall be sufficient to allow a repackager or dispenser to select an adequate container and shall include a description of the composition of the container(s), e.g., glass, polyethylene, polyvinyl chloride, and any moisture vapor transmission rate characteristics required. The labeling shall also indicate whether or not the container is to afford light protection, and shall include any storage or shipping temperature restrictions to which the drug as repackaged shall be limited (see 21 CFR 201.100).■1S (*USP27*)

Labeling—The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.

Amount of Ingredient per Dosage Unit—The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in *Deliverable Volume* ⟨698⟩. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see *Percentage Measurements*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also *Units of Potency* in these *General Notices*).

Use of Leading and Terminal Zeros—In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

Labeling of Salts of Drugs—It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-Containing Products—The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

Labeling Parenteral and Topical Preparations—The label of a preparation intended for parenteral or topical use states the names of all added substances (see *Added Substances* in these *General Notices and Requirements*, and see *Labeling* under *Injections* ⟨1⟩), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes—The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol—The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C_2H_5OH.

Special Capsules and Tablets—The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.

Expiration Date and Beyond-Use Date—The label of an official drug product, nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary con-

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ditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," or "Expires 6/89"). [NOTE—For additional information and guidance, refer to the Nonprescription Drug Manufacturers Association's *Voluntary Codes and Guidelines of the OTC Medicines Industry.*]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article must not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the *General Notices and Requirements* of this Pharmacopeia. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution prior to use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be one year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturers container, whichever is earlier, unless stability data or the manufacturers labeling indicates otherwise.

The dispenser must maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than 25°. The plastic material used in packaging the dosage forms must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records must be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

Pharmaceutical Compounding—The label on the container or package of an official compounded preparation shall bear a beyond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, is to be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see *Stability Criteria and Beyond-Use Dating* under *Stability of Compounded Preparations* in the general tests chapter

■*Pharmacy Compounding* ⟨795⟩).■2S (*USP26*)

MONOGRAPHS (USP)

BRIEFING

Albendazole Oral Suspension, *USP 26* page 54 and page 2505 of *PF* 27(3) [May–June 2001]. USP acknowledges that *Albendazole Oral Suspension* is approved in several countries for human use. It is proposed to change the specified labeling requirements so that manufacturers can use the USP *Albendazole Oral Suspension* monograph for these drug products.

(NL: W. Paul) RTS—39499-1

Change to read:

Packaging and storage—Preserve in tight containers,

▲and store▲*USP27*
at controlled room temperature.

Change to read:

Labeling—~~Label it to indicate that it is for veterinary use only.~~

■Oral Suspension intended for veterinary use only is so labeled.■1S (*USP27*)

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BRIEFING

Albumin Human, *USP 26* page 55 and page 43 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Chromatography* ⟨621⟩.

(HDQ: M. Marques) RTS—39943-5

Change to read:

~~» Albumin Human conforms to the regulations of the federal Food and Drug Administration concerning biologics (640.80 to 640.86) (see *Biologics* ⟨1041⟩). It is a sterile, nonpyrogenic preparation of serum albumin obtained by fractionating material (source blood, plasma, serum, or placentas) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen.~~

■» Albumin Human is a sterile, nonpyrogenic preparation of serum albumin obtained by fractionating material (source blood, plasma, serum, or placentas) from healthy human donors, the source material being tested for the absence of hepatitis B surface antigen, hepatitis C, and HIV by antibody and nucleic acid assay, and other disease-causative agents that are not destroyed or removed by the processing method, as determined by the medical history of the donor, and from such physical examination and approved clinical tests as may appear necessary for each donor at the time the blood was obtained.■1S (*USP27*)
It is made by a process that yields a product that is safe for intravenous use. Not less than 96 percent of its total protein is albumin

■, as determined by an approved and validated method.■1S (*USP27*)
It is a solution containing, in each 100 mL, either 25 g of serum albumin osmotically equivalent to 500 mL of normal human plasma, or 20 g equivalent to 400 mL, or 5 g equivalent to 100 mL, or 4 g equivalent to 80 mL thereof, and contains not less than 93.75 percent and not more than 106.25 percent of the labeled amount in the case of the solution containing 4 g in each 100 mL, and not less than 94.0 percent and not more than 106.0 percent of the labeled amount in the other cases. It contains no added antimicrobial agent, but may contain sodium acetyltryptophanate with or without sodium caprylate as a stabilizing agent. ~~It has a sodium content of not less than 130 mEq per liter and not more than 160 mEq per liter. It has a heme content such that the absorbance of a solution, diluted to contain 1 percent of protein, in a 1-cm holding cell, measured at a wavelength of 403 nm, is not more than 0.25. It meets the requirements of the tests for heat stability and for pH.~~

■■1S (*USP27*)

Change to read:

Packaging and storage—Preserve in tight containers, and store at the temperature ~~recommended by the manufacturer~~

■■1S (*USP27*)
indicated on the label.

Change to read:

Expiration date—The expiration date is not later than 5 years after issue from manufacturer's cold storage ~~(5°, 3 years)~~

■(at 5° for not more than 3 years)■1S (*USP27*)
if labeling recommends storage between 2° and 10°; not later than 3 years after issue from manufacturer's cold storage ~~(5°, 3 years)~~

■■1S (*USP27*)
if labeling recommends storage at temperatures not higher than 37°; and not later than 10 years after date of manufacture if in a hermetically sealed metal container and labeling recommends storage between 2° and 10°.

Change to read:

Labeling— ~~Label it to state that it is not to be used if it is turbid and that it is to be used within 4 hours after the container is entered. Label it also to state the osmotic equivalent in terms of plasma, the sodium content, and the type of source material (venous plasma, placental plasma, or both) from which it was prepared. Label it also to indicate that additional fluids are needed when the 20 g per 100 mL or 25 g per 100 mL product is administered to a markedly dehydrated patient.~~

■Label it to state (1) the osmotic equivalent in terms of plasma, and the sodium content in terms of a value or a range in mEq per liter, (2) the need for additional fluids when 20% or 25% albumin is administered to a patient with marked dehydration, and (3) the protein content, expressed as a 4%, 5%, 20%, or 25% solution. Include on the label in a prominent position the following cautionary statements: "Do Not Use if Turbid. Do Not Begin Administration More Than 4 Hours After the Container Has Been Entered." Indicate on either the container or package label, or in the package insert, the type of source material, expressed as venous plasma, pla-

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cental plasma, or both, used to manufacture the final product. Label it to indicate the volume of the preparation, storage conditions, the expiration date, and the name and concentration of any added substance (for example, stabilizer). Where applicable, the label indicates that the preparation is suitable for administration to patients undergoing dialysis and to premature infants.■1S (*USP27*)

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Albumin Human RS. USP Endotoxin RS.*■1S (*USP27*)

Add the following:

■**Identification**—

A: *Immunodiffusion*—

pH 8.0 buffer—Dissolve 1.98 g of barbituric acid, 1.03 g of sodium barbital, and 8.7 g of sodium chloride in 900 mL of water. Adjust with a sodium hydroxide solution to a pH of 8.0, dilute with water to make up to 1 L, and mix.

Procedure—Prepare agar-gel immunodiffusion plates each containing one central well and 5 or 6 outer wells concentric with the central well using 1.9 g of agar in 150 mL *pH 8.0 buffer*. Place 5 µL of Albumin Human in the central well of one plate and 5 µL of USP Albumin Human RS in the central well of another plate. Add 5 µL of an antiserum specific to human plasma proteins from a suitable commercial source in one of the appropriately marked outer wells of each plate. Place 5 µL each of antisera specific to plasma proteins of animals commonly used in the preparation of materials of biological origin in other appropriately marked outer wells of each plate. [NOTE—At the minimum, antisera against plasma proteins of bovine, porcine, and ovine must be used.] Incubate the plates at 2° to 8° for at least 24 hours. The plate containing Albumin Human observed in a bright white light shows a sharp white arc between the central well and the well containing antiserum specific to human plasma proteins, and no arc between the central well and the wells containing antisera specific to plasma proteins of other animals. The test is valid if the plate containing USP Albumin Human RS shows an arc between the central well and the well containing antiserum specific to human plasma proteins, and no arc between the central well and the wells containing antisera specific to plasma proteins of other animals.

B: *Immunoelectrophoresis*—

Electrophoretic buffer—Dissolve 2.5 g of barbituric acid, 16.7 g of sodium barbital, 1.0 g of sodium chloride, and 0.7 g of edetate disodium in about 1.9 L of water, and adjust with hydrochloric acid or sodium hydroxide solution to a pH of 8.6. Dilute with water to obtain a final volume of 2 L, and mix.

Reference solution—Dilute normal human serum from a suitable commercial source with *Electrophoretic buffer* to obtain a total protein concentration of about 10 mg per mL.

Test solution—Dilute Albumin Human with *Electrophoretic buffer* to obtain a total protein concentration of about 10 mg per mL.

Procedure—Mount a suitable immunoelectrophoresis microslide strip containing 1% agar gel between the two buffer reservoirs of a suitable microelectrophoresis apparatus. Place suitable volumes of *Electrophoretic buffer* in the buffer reservoirs. Cut two pieces of blotting paper of suitable lengths such that the widths are approximately equal to that of the agar gel, and soak them in *Electrophoretic buffer*. Place the pieces such that one end of each dips into the *Electrophoretic buffer* while the other ends of the pieces are placed on the two ends of the agar-gel strip such that they extend for about 1 cm at both ends. Using a suitable commercial device dig two wells about 1.5 cm apart near one end of the agar-gel strip such that they are about 0.5 cm away from the nearest blotting paper and at the same level perpendicular to the direction of the electrophoresis, and dig a central slot of suitable length between the two wells, and

equidistant from them, along the direction of electrophoresis. Place 1 µL of *Reference solution* into one well and an equal volume of *Test solution* into the other. Electrophorese the samples for about 35 minutes applying 90 volts across the agar-gel strip. Remove the blotting papers, and place in the central slot about 25 µL of the same antiserum specific to human plasma proteins as is used in *Identification* test *A*. Incubate the microslide at 2° to 8° for at least 24 hours. Observed in a bright white light, the microslide shows an arc for *Test solution* that corresponds to the major arc obtained with the *Reference solution*. The test is not valid if *Identification* test *A* is not valid.■1S (*USP27*)

Add the following:

■**Bacterial endotoxins** ⟨85⟩—It contains not more than 0.5 USP Endotoxin Unit per mL.■1S (*USP27*)

Add the following:

■**Safety**—It meets the requirements when tested as directed for *Safety Tests—Biologicals* under *Biological Reactivity Tests, In Vivo* ⟨88⟩■1S (*USP27*)

Add the following:

■**Sterility**⟨71⟩: It meets the requirements.■1S (*USP27*)

Add the following:

■**pH** ⟨791⟩: between 6.4 and 7.4 when diluted with 0.15 M sodium chloride to obtain a solution containing 1% protein.■1S (*USP27*)

Add the following:

■**Molecular size distribution**—

Mobile phase—Prepare a suitable degassed and filtered solution containing 7.337 g of dibasic sodium phosphate heptahydrate, 1.741 g of monobasic sodium phosphate monohydrate, and 11.688 g of sodium chloride per liter in water.

Reference solution—Dilute a solution of USP Albumin Human RS in *Mobile phase* to obtain a solution having a concentration of about 10 mg per mL of protein, and mix.

Test solution—Dilute a solution of Albumin Human in *Mobile phase* to obtain a solution having about the same concentration of protein as the *Reference solution*, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a UV/visible detector set at 280 nm, a 7.5- × 600-mm analytical column, a 7.5- × 75-mm guard column, both containing ~~L58~~ L## (see *Chromatography* ⟨621⟩) packing, and maintained at ambient temperature. The flow rate is constant and is maintained at 0.5 mL per minute ± 1%.

Procedure—Separately inject 25 µL of the *Reference solution* and the *Test solution*, and record the chromatograms. The area of the major peak is not less than 85% of the total peak area in the chromatogram. The test is not valid unless the value obtained for USP Albumin Human RS is within the value stated in the USP Albumin Human RS Data Sheet.■1S (*USP27*)

Add the following:

■**Heat stability**—A final container sample of Albumin Human shall remain unchanged, as determined by visual inspection, after heating at 57° for 50 hours, when compared to its control consisting of a sample, from the same lot, which has not undergone the heat treatment.■1S (*USP27*)

Add the following:

■**Prekallikrein activator**—

Buffer A—Dissolve 6.1 g of tris(hydroxymethyl)aminomethane, 1.2 g of sodium chloride, 50 mg of hexadimethrine bromide, and 0.1 g of sodium azide in 800 mL water. Adjust with 2 M hydrochloric acid at 20° to 25° to a pH of 7.8, and dilute with water to 1000 mL.

Buffer B—Dissolve 6.1 g of tris(hydroxymethyl)aminomethane and 0.7 g of sodium chloride in 800 mL of water. Adjust with 2 M hydrochloric acid at 20° to 25° to a pH of 7.8, and dilute with water to 1000 mL.

Chromogenic substrate solution A—Prepare a solution of a suitable *Chromogenic Substrate for Amidolytic Test* (see *Reagent Specifications* under *Reagents, Indicators, and Solutions*) specific for kallikrein in water to obtain a solution having a concentration of about 6 mM.

Chromogenic substrate solution B—Dilute 1 volume of *Chromogenic substrate solution A* with 9 volumes of *Buffer B*.

Prekallikrein substrate—[NOTE—To avoid coagulation activation, blood or plasma used for the preparation of *Prekallikrein substrate* must only come into contact with plastic or silicone-treated glass surfaces.] Draw 9 volumes of human blood into 1 volume of a suitable anticoagulant solution containing 1 mg per mL of hexadimethrine bromide. Centrifuge the mixture at 3600 *g* for 5 minutes. Centrifuge the plasma fraction again at 6000 *g* for 20 minutes to sediment platelets. Dialyze the platelet-reduced plasma against 10 volumes of *Buffer A* for 20 hours. Apply the dialyzed plasma to a DEAE-agarose column equilibrated in *Buffer A*, such that the volume of DEAE-agarose is twice the volume of the plasma. Elute from the column with *Buffer A* at 20 mL per cm^2 per hour. Collect the eluate in fractions, and record the absorbance at 280 nm. Pool the fractions containing the first protein peak so that the volume of the pool is about 1.2 times the volume of the platelet-reduced plasma. Add solid sodium chloride to the pooled solution, and dissolve such that the final concentration of sodium chloride is 7.0 mg per mL. Filter the solution using a membrane filter having a 0.45-µm porosity, freeze the filtrate in portions, and store at –70°; the substrate is stable at –70° for 1 year. [NOTE—Carry out all steps from the beginning of the chromatography to freezing in portions during a single working day.] Test the substrate pool for absence of kallikrein activity by mixing 1 part with 20 parts of the *Chromogenic substrate solution B* prewarmed at 37°, and incubate at 37° for 2 minutes. The substrate is suitable if the increase in absorbance is less than 0.001 per minute.

Standard solutions—Dilute USP Albumin Human RS with *Buffer B* to prepare four solutions corresponding to a suitable range of prekallikrein activator concentration in IU per mL.

Test solution—Dilute Albumin Human with an equal volume of *Buffer B*.

Procedure—To suitably capped tubes transfer 25 µL each of *Buffer B* (to be used as the blank), four *Standard solutions*, and the *Test solution*. To each tube add 100 µL of *Prekallikrein substrate*, and incubate at 37° for 45 minutes. Transfer 25 µL of each solution to a suitable cuvette (1-cm path length) containing 1000 µL of *Chromogenic substrate solution B* and prewarmed and maintained at 37°. Mix, and measure the change of absorbance (ΔA) for 10 minutes spectrophotometrically at 405-nm wavelength at 37°. Subtract ΔA per minute for the blank from ΔA per minute for each of the *Standard solutions*, and the *Test solution*. Plot the corrected ΔA per minute for each of the *Standard solutions* versus its respective prekallikrein activator concentration. Calculate the prekallikrein activator concentration of the *Test solution* from the standard curve, and multiply the value by 2. The prekallikrein activator concentration of Albumin Human is not more than 35 IU per mL.■1S (*USP27*)

Add the following:

■**Protein content**—

Sodium molybdate solution—Dissolve 9.0 g of disodium molybdate dihydrate in 115 mL of water in a suitable container. Add 4 mL of sulfuric acid, and mix.

Test solution—Dilute Albumin Human with 0.15 M sodium chloride to obtain a solution containing about 7.5 mg of protein per mL of the solution.

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Blank: 0.15 M sodium chloride used to make the *Test solution*.

Procedure—To 2.0 mL of the *Test solution* and the *Blank* in suitable centrifuge tubes, add 2.0 mL of *Sodium molybdate solution*. Mix, allow to stand for about 10 minutes, centrifuge for 5 minutes, and decant the supernatant. Resuspend the precipitates in 2.0 mL of *Sodium molybdate solution*, centrifuge for 5 minutes, decant the supernatant, and hold the tubes inverted to drain on a filter paper. Transfer the residues quantitatively with a minimum quantity of water to a micro-Kjeldahl flask, and determine the nitrogen in the residues using *Method II* under *Nitrogen Determination* ⟨461⟩. Multiply the result, corrected for the *Blank*, by 6.25 to calculate the quantity of protein.■1S (*USP27*)

Add the following:

■**Heme content**—Dilute Albumin Human using 0.15 M sodium chloride to obtain a solution having a concentration of 10 mg per mL of protein. The absorbance (see *Spectrophotometry and Light-Scattering* ⟨851⟩) of the solution measured at 403 nm using 0.15 M sodium chloride as the blank, is not greater than 0.25.■1S (*USP27*)

Add the following:

■**Potassium content**—

Standard solutions 1, *2*, *3*, and *4*—Prepare four standard solutions containing 0, 1.0, 2.0, and 3.0 mg of potassium, in the form of the chloride, per L, respectively, in 0.1 N hydrochloric acid and 25 mEq of sodium (1.46 g of sodium chloride) per L.

Test solution—Transfer 3.5 mL of Albumin Human, 5.0 mL of 0.15 M sodium chloride, and 5.0 mL of 1 N hydrochloric acid to a 50-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Set a suitable flame photometer to a wavelength of 766 nm. Adjust the instrument to zero transmittance with *Standard solution 1* and to 100% transmittance with *Standard solution 4*. Read the percent transmittance of *Standard solutions 2* and *3*. Plot the observed transmittance of *Standard solutions 2, 3,* and *4* versus their respective potassium concentrations. Adjust the instrument to zero transmittance with *Standard solution 1* and to 100% transmittance with *Standard solution 4*. Read the percent transmittance of the *Test solution*, and from the standard curve calculate the potassium content in mg per liter of the *Test solution*. Multiply the value by 0.365 (multiplication by the dilution factor and division by the equivalent weight of potassium, 39.1) to obtain the potassium concentration in mEq per L in the sample. Albumin Human contains between 0 and 1 mEq of potassium per L of sample.■1S (*USP27*)

Add the following:

■**Sodium content**—

Standard solutions 1, *2*, *3*, and *4*—Prepare four standard solutions containing 0, 2.0, 3.0, and 4.0 mg of sodium, in the form of the chloride, per L, respectively, in 0.1 N hydrochloric acid and 6.0 mEq of potassium (447.6 mg of potassium chloride) per L.

Test solution—Transfer 75 µL of Albumin Human, 4.0 mL of 0.15 M potassium chloride, and 10.0 mL of 1 N hydrochloric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Set a suitable flame photometer to a wavelength of 589 nm. Adjust the instrument to zero transmittance with *Standard solution 1* and to 100% transmittance with *Standard solution 4*. Read the percent transmittance of *Standard solutions 2* and *3*. Plot the observed transmittance of *Standard solutions 2, 3,* and *4* versus their respective sodium concentrations. Adjust the instrument to zero transmittance with *Standard solution 1* and to 100% transmittance with *Standard solution 4*. Read the percent transmittance of the *Test solution*, and from the standard curve calculate the sodium content in mg per liter in the *Test solution*. Multiply the value by 57.97 (multiplication by the di-

lution factor and division by the equivalent weight of sodium, 23.0) to obtain the sodium concentration in mEq per L. Albumin Human contains between 130 and 160 mEq of sodium per L of sample.■1S (*USP27*)

BRIEFING

Alendronic Acid Tablets, page 740 of *PF* 28(3) [May–June 2002]—See briefing under *Chromatography* ⟨621⟩).

(HDQ: M. Marques) RTS—39943-1

Add the following:

■~~Alendronate Sodium Tablets~~ Alendronic Acid Tablets

» ~~Alendronate Sodium Tablets contain~~ Alendronic Acid Tablets contain an amount of Alendronate Sodium, equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ~~alendronate sodium ($C_4H_{12}NNaO_7P_2 \cdot 3H_2O$).~~ alendronic acid ($C_4H_{13}NO_7P_2$).

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Alendronate Sodium RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: ~~30~~ 15 minutes.

~~Determine the amount of $C_4H_{12}NNaO_7P_2 \cdot 3H_2O$ dissolved by employing the following method.~~

~~*Buffer solution* and *Mobile phase*—Prepare as directed in the *Assay.*~~

~~*0.05% 9-Fluorenylmethyl chloroformate solution*—Transfer 100 mg of 9-fluorenylmethyl chloroformate to a 200-mL volumetric flask, dilute with acetonitrile to volume, and mix. This solution must be freshly prepared.~~

~~*Borate solution*—Transfer 38.1 g of sodium borate to a 1-liter volumetric flask, dissolve in and dilute with water to volume, and mix.~~

~~*Borate buffer*—Dissolve 6.2 g of boric acid in approximately 950 mL of water, adjust with 1 N sodium hydroxide to a pH of 9.0, and dilute with water to 1 liter.~~

~~*Diluent*—Transfer 176.4 g of sodium citrate dihydrate to a 1000-mL volumetric flask, dissolve in and dilute with *Dissolution Medium* to volume, and mix.~~

~~*Standard stock solution*—Dissolve an accurately weighed quantity of USP Alendronate Sodium RS in *Dissolution Medium*, and dilute quantitatively and stepwise with the same solvent to obtain a solution having a known concentration corresponding to the concentration that would be obtained by dissolving one Tablet in 900 mL of the same *Medium.*~~

~~*Standard solution*—Transfer 5.0 mL of the *Standard stock solution* to a 50-mL polypropylene screw-cap centrifuge tube containing 1.0 mL of *Diluent* and 5.0 mL of *Borate solution buffer*, and mix for about 3 minutes. Add 3.0 mL of *0.05% 9-Fluorenylmethyl chloroformate solution*, and agitate for about 30 seconds. Allow the solution to stand at room temperature for 25 minutes. Add 25 mL of methylene chloride, and agitate for about 40 seconds. Centrifuge the mixture for 10 minutes. Use a portion of the clear upper aqueous layer.~~

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~~*Reagent blank*—Using 5 mL of water, proceed as directed for *Standard solution*, beginning with "to a 50-mL polypropylene screw-cap centrifuge tube."~~

~~*Test solution*—After 30 minutes, withdraw a portion of the solution under test, and filter immediately. Using 5.0 mL of the filtrate, proceed as directed for *Standard solution*, beginning with "to a 50-mL polypropylene screw-cap centrifuge tube."~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the capacity factor, *k′*, is not less than 2.0; the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 50 µL) of the *Standard solution*, the *Test solution*, and the *Reagent blank* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of alendronate sodium ($C_4H_{12}NNaO_7P_2 \cdot 3H_2O$) dissolved by the formula:~~

~~$$0.9C(r_u/r_s),$$~~

~~in which C is the concentration, in µg per mL, of USP Alendronate Sodium RS in the *Standard stock solution;* and r_u and r_s are the peak responses obtained from the *Test solution* and the *Standard solution*, respectively.~~

Procedure—Determine the amount of $C_4H_{13}NO_7P_2$ dissolved, by employing the procedure set forth in the *Assay*, except to make any necessary volumetric adjustment and to use 200-µL injection volumes.

Tolerances—Not less than 80% (Q) of the labeled amount of ~~$C_4H_{12}NNaO_7P_2 \cdot 3H_2O$~~ alendronic acid ($C_4H_{13}NO_7P_2$) is dissolved in ~~30 minutes~~ 15 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Limit of phosphate—

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

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of alendronic acid, to a 50-mL volumetric flask, dissolve in HPLC grade water, sonicate for 30 minutes, and shake for 10 minutes. Dilute with HPLC grade water to volume, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Procedure—Inject a volume (about 100 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of phosphate in the portion of Tablets taken by the formula:

$$100(r_i/r_s),$$

in which r_i is the phosphate peak response, and r_s is the sum of the responses of all the peaks: not more than 0.1% is found.

Assay—

~~*Diluent*—Transfer 29.4 g of sodium citrate dihydrate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.~~

~~*Buffer solution*—Transfer 14.7 g of sodium citrate dihydrate and 7.05 g of anhydrous dibasic sodium phosphate to a 1000-mL volumetric flask, dissolve in about 900 mL of water, adjust with phosphoric acid to a pH of 8.0, dilute with water to volume, and mix.~~

~~*0.1% 9-Fluorenylmethyl chloroformate solution*—Transfer 250 mg of 9-fluorenylmethyl chloroformate to a 250-mL volumetric flask, dilute with acetonitrile to volume, and mix. Prepare this solution fresh just prior to use.~~

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~~*Borate solution*—Transfer 38.1 g of sodium borate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Prepare a 0.1 M sodium borate solution.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of *Buffer solution*, acetonitrile, and methanol (75:20:5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard stock preparation*—Transfer about 25 mg of USP Alendronate Sodium RS, accurately weighed, to a 1000-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.~~

~~*Standard preparation*—Transfer 5.0 mL of the *Standard stock preparation* to a 50-mL polypropylene screw-cap centrifuge tube containing 5 mL of *Borate solution*, and mix for about 3 minutes. Add 4 mL of *0.1% 9-Fluorenylmethyl chloroformate solution*, and agitate for about 30 seconds. Allow the solution to stand at room temperature for 25 minutes. Add 25 mL of methylene chloride, and agitate for about 40 seconds. Centrifuge the mixture for 10 minutes. Use the clear upper aqueous layer.~~

~~*Assay preparation*—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 25 mg of alendronate sodium, to a 1000-mL volumetric flask, dilute with *Diluent* to volume, and mix. Stir with the aid of a magnetic stirrer for 30 minutes. Centrifuge a portion of this solution for about 20 minutes. Using 5.0 mL of the solution so obtained, proceed as directed for *Standard preparation*, beginning with "to a 50-mL polypropylene screw-cap centrifuge tube."~~

~~*Reagent blank*—Using 5 mL of *Diluent*, proceed as directed for *Standard preparation*, beginning with "to a 50-mL polypropylene screw-cap centrifuge tube."~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 266-nm detector and a 4.1-mm × 25-cm column that contains 10-µm packing L21. The column is maintained at a constant temperature of about 35°. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the capacity factor, k', is not less than 2.0; the column efficiency is not less than 1500 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 50 µL) of the *Standard preparation*, *Assay preparation*, and the *Reagent blank* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of alendronate sodium ($C_4H_{12}NNaO_7P_2 \cdot 3H_2O$), in the portion of Tablets taken by the formula:~~

$$W(r_U/r_S),$$

~~in which W is the weight, in mg, of USP Alendronate Sodium RS taken to prepare the *Standard stock preparation*; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

Mobile phase—Prepare a 7.2 mM solution of nitric acid in HPLC grade water.

System suitability solution—Prepare a solution of USP Alendronate Sodium RS and sodium biphosphate in HPLC grade water containing 0.2 mg per mL and 0.1 mg per mL, respectively.

Standard preparation—Prepare a solution of USP Alendronate Sodium RS in HPLC grade water having a known concentration of about 0.52 mg of alendronate sodium trihydrate per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of alendronic acid, to a 250-mL volumetric flask, dissolve in HPLC grade

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water, sonicate for 30 minutes, and shake for 10 minutes. Dilute with HPLC grade water to volume, and mix. Pass a portion of this solution through a filter having a 0.45-mm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.1-mm × 25-cm column that contains packing ~~L53.~~ L## (see *Chromatography* ⟨621⟩). The flow rate is about 1.6 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between alendronate and phosphate is not less than 2.0; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of alendronic acid ($C_4H_{13}NO_7P_2$) in the portion of Tablets taken by the formula:

$$250(249.10/325.12)C(r_U/r_S),$$

in which 249.10 and 325.12 are the molecular weights of alendronic acid and alendronate sodium trihydrate, respectively; *C* is the concentration, in mg per mL, of alendronate sodium trihydrate in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Allopurinol Oral Solution, page 1991 of *PF* 28(6) [Nov.–Dec. 2002]; **Atenolol Oral Solution,** page 1991 of *PF* 28(6) [Nov.–Dec. 2002]. These two new monographs, which previously appeared in *Pharmacopeial Previews*, are now recommended to be published as four monographs, with changes, in *In-Process Revision* for inclusion in *USP*. The Expert Committee on Nomenclature and Labeling voted to approve the separate titles in the general form [DRUG] Oral Solution and [DRUG] Oral Suspension to alleviate confusion if a preparation called "Oral Solution" could in fact be a suspension with "shake well" instructions where tablets formulated with insoluble excipients provide the prescribed amount of the therapeutically active ingredient.

The revised titles "Vehicle for Oral Solution" and "Vehicle for Oral Suspension" are indicated in the compounding directions, and control of pH is recommended similarly as for the monographs on the vehicles.

(CRX: C. Okeke; NL: C. Barnstein) RTS—39822-1

Add the following:

■Allopurinol Oral ~~Solution~~ Suspension

» Allopurinol Oral ~~Solution~~ Suspension contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of allopurinol ($C_5H_4N_4O$). Prepare Allopurinol Oral ~~Solution~~ Suspension at a 2% concentration, for example, as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Allopurinol	2 g
Glycerin	5 mL
~~Oral Suspension Vehicle~~ Vehicle for Oral Suspension	45 mL
~~Oral Solution Vehicle,~~ Vehicle for Oral Solution, a sufficient quantity to make	100 mL

~~Calculate~~ Select the number of Tablets that contain the specified amount of Allopurinol and calculate the quantity of each ingredient required for the total amount to be prepared. Accurately count/weigh/measure each ingredient.~~, or obtain~~

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~~the required number of Tablets.~~ Thoroughly pulverize the tablets.~~, if used.~~ Mix the ~~Allopurinol~~ powdered Allopurinol Tablets and Glycerin to form a smooth paste, incorporate the ~~Oral Suspension Vehicle,~~ Vehicle for Oral Suspension, add sufficient ~~Oral Solution Vehicle~~ Vehicle for Oral Solution to volume, and mix well. Adjust the pH, if necessary. Package, and label.

Packaging and storage—Package in a tight container, and store at controlled room temperature.

Labeling—Label it to state that it is to be shaken well before use and that it is to be discarded after 60 days. Label it to state that it is to be kept out of the reach of children. Label it to indicate the nominal content of Allopurinol ~~Oral Solution.~~ in the Oral Suspension.

pH ⟨791⟩: an apparent pH between 6.5 and 7.5.

Beyond-use date: not more than 60 days after preparation.■1S (*USP27*)

BRIEFING

Atenolol Oral Solution, page 1991 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Allopurinol Oral Solution*.

(CRX: C. Okeke; NL: C. Barnstein) RTS—39822-2

Add the following:

■Atenolol Oral Solution

» Atenolol Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of atenolol ($C_{14}H_{22}N_2O_3$).

Prepare Atenolol Oral Solution at a 0.2% concentration, for example, as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩):

Atenolol	200 mg
Glycerin	5 mL
~~Oral Suspension Vehicle~~ Vehicle for Oral Suspension	45 mL
~~Oral Solution Vehicle Sugar Free~~ Vehicle for Oral Solution, Sugar Free, a sufficient quantity to make	100 mL

Calculate the quantity of each ingredient required for the total volume and atenolol strength to be prepared. Accurately weigh/measure each ingredient. ~~Atenolol Oral Solution (0.2%) may be prepared from Atenolol powder or pulverized tablets or Atenolol Tablets.~~ Mix the Atenolol, previously pulverized, and Glycerin to form a smooth paste. Incorporate the ~~Oral Suspension Vehicle if Atenolol Tablets are used to prepare the Oral Solution. The Oral Suspension Vehicle may be omitted if Atenolol is dissolved to prepare the Oral Solution.~~ Vehicle for Oral Suspension or an equal volume of Vehicle for Oral Solution, Sugar Free. [NOTE—The Vehicle for Oral Suspension may be omitted.] Incorporate sufficient ~~Oral Solution Vehicle~~ Vehicle for Oral Solution, Sugar Free in increments to

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bring to volume, and mix well. Adjust the pH, if necessary. [NOTE—Do not use a sucrose-containing vehicle for oral solution.] Package, and label.

Packaging and storage—Package in amber, tight containers, and store at controlled room temperature.

Labeling—Label it to state that it is to be shaken well before use, and discarded after 60 days. Label it to state that it is to be kept out of reach of children. Label it to indicate the nominal atenolol concentration.

Beyond-use date: not more than 60 days after preparation.■IS (*USP27*)

BRIEFING

Anthrax Vaccine Adsorbed. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The approved U.S. Reference Anthrax Vaccine to be used in the test for *Relative potency*, included in the proposed monograph, is available from the Center for Biologics Evaluation and Research, Food and Drug Administration.

(VVI: L. Bhattacharyya) RTS—37388-1; 39647-1; 39509-1; 39972-1

Add the following:

■Anthrax Vaccine Adsorbed

» Anthrax Vaccine Adsorbed is a sterile, milky-white suspension made from cell-free filtrates of microaerophilic cultures of an avirulent, non-encapsulated strain of *Bacillus anthracis*. The final product contains no dead or live bacteria. The production cultures are grown in a chemically defined protein-free medium containing amino acids, vitamins, inorganic salts, and sugars. The sterile filtrate is adsorbed on sterile aluminum hydroxide, concentrated 10-fold, and resuspended in sterile physiological saline containing formaldehyde with benzethonium chloride as a preservative. Sublots may be combined to produce final lots. The product meets potency requirements when tested against the U.S. Reference Standard Anthrax Vaccine, in accordance with approved procedures (guinea pig intracutaneous challenge models).

Packaging and storage—Preserve in multiple-dose tight Type I glass containers, and store at a temperature between 2° and 8°. Do not freeze.

Expiration date—The expiration date is 18 months from the date of manufacture.

Labeling—Label it to state that it is to be well shaken before use and that it is not to be frozen. Label it to state that it is "Rx only" and not to be used after the expiration date given on the package.

FILTRATE—

Identification—

Trichloroacetic acid solution—Prepare a solution of trichloroacetic acid (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) in water containing 100 g trichloroacetic acid per 100 mL of the solution.

Sample buffer—Prepare a solution containing 141 mM tris(hydroxymethyl)aminomethane, 106 mM tris(hydroxymethyl)aminomethane hydrochloride, 0.51 mM edetate disodium, 2% (w/v) dodecyl lithium sulfate, 10% (v/v) glycerol, 0.22 mM Coomassie blue G-250, and 0.175 mM phenolsulfonphthalein. If necessary, adjust with hydrochloric acid or sodium hydroxide to a pH of 8.5.

Running buffer—Prepare a solution containing 25 mM tris(hydroxymethyl)aminomethane, 192 mM glycine, and 0.1% (w/v) dodecyl sodium sulfate (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) in water. If necessary, adjust with hydrochloric acid or sodium hydroxide to a pH of 8.5.

Transblotting buffer—Prepare a solution containing 12.5 mM tris(hydroxymethyl)aminomethane, 96 mM glycine, and 10% (v/v) methanol. If necessary, adjust with hydrochloric acid or sodium hydroxide to a pH of 8.0.

Blocking buffer—Prepare a solution containing 10 mM monobasic sodium phosphate, 150 mM sodium chloride, 5% (w/v) nonfat dry milk, and 0.05% (w/v) Polysorbate 20. Adjust with sodium hydroxide to a pH of 7.4.

Primary antibody solutions—Prepare suitable monoclonal antibodies raised against the Protective Antigen (PA), the Lethal Factor (LF), and the Edema Factor (EF), respectively, of *Bacillus anthracis* in murine ascites cells, harvested, and used without further purification. Immediately before use, dilute each of the murine ascites fluids containing the monoclonal antibodies 1:1000 (v/v) with the *Blocking buffer.*

Secondary antibody solution—Immediately before use, dissolve according to the manufacturer's instructions, if necessary, and dilute the stock horseradish peroxidase conjugated to goat anti-mouse IgG solution 1:1000 with *Blocking buffer.*

Chromogenic visualization solution—Prepare a 150 mg per mL solution of 4-chloro-1-naphthol in water.

Test solution—Use Anthrax Vaccine Filtrate as is.

Procedure—In a suitable centrifuge tube transfer 30/*c* mL of the *Test solution*, where *c* is the total protein concentration, in µg per mL, of the solution as determined in the test for *Total protein*. Add 16.5/*c* mL of *Trichloroacetic acid solution*, and incubate for at least 10 minutes. Centrifuge at 9,000*g* for about 10 minutes, decant off the supernatant, and hold the tube inverted to drain on a filter paper. Dissolve the pellet in about 60 µL of *Sample buffer*, and transfer the solution to a polypropylene microfuge tube that has a lid. Close the lid tightly, secure with a lid-lock, and heat at 100° for 5 minutes. Allow the solution to cool to room temperature, and centrifuge at 10,000*g* for 15 seconds to collect the liquids. In a suitable device for polyacrylamide-gel electrophoresis (see *Electrophoresis* ⟨726⟩ and the section *Polyacrylamide Gel Electrophoresis* under *Biotechnology-Derived Articles—Tests* ⟨1047⟩) add appropriate volumes of the *Running buffer* in the upper and the lower buffer chambers. Attach a 4%–20% gradient tris-glycine polyacrylamide slab gel sandwiched between two glass plates, such that the wells for sample application are exposed to the *Running buffer* in the upper buffer chamber. Apply about 20-µL aliquots of the treated *Test solution* in three alternate lanes. [NOTE—Do not apply any solution in the outside lanes.] Connect the lower buffer chamber electrode to the positive terminal and the upper buffer chamber electrode to the negative terminal of a suitable power supply unit, and carry out the electrophoresis at a constant current of about 40 mA. When the dye-front is about 1 cm from the bottom of the gel (about 40 minutes), stop the current, and remove the gel from the gel assembly. [NOTE—Do not touch the gel with bare hand. Use gloves.]

Place 3–4 filter papers (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*), cut to the size of the gel and soaked in the *Transblotting buffer*, on the anode plate of a suitable semidry electroblotter. Cut a nitrocellulose membrane to the same size as the gel plus 1–2 mm on each side, and "wet" the membrane by immersing it into the *Transblotting buffer* for about 15 seconds, such that there is no air-bubble between the buffer and the membrane. Place the "wet" membrane immediately on the stack of filter papers, and remove all air bubbles between the membrane and

filter paper by rolling a pipet, or equivalent, gently over the surface of the membrane. Place a few drops of the *Transblotting buffer* on the membrane, and then carefully place the gel on it. Gently roll a pipet, or equivalent, over the surface of the gel to ensure intimate contact between the gel and the membrane, making sure that there are no air bubbles in between. Place a filter paper cut to the size of the gel and soaked in the *Transblotting buffer*, such that there is no air-bubble between the filter paper and the gel. Place 2–3 additional filter papers, prepared in a similar manner, on the top, and complete the transfer stack by placing the cathode plate on the top. Apply a current of about 250 mA, and continue transfer for 90 minutes.

Remove the membrane, and wash it quickly by immersing into water for 15 seconds. [NOTE—Do not touch the membrane with bare hand. Use gloves.] Cut the membrane into three strips such that each strip contains a lane containing the *Test solution*, and mark the strips as PA, LF, and EF at the top. Place each strip in a heat-sealable bag, add 5 mL of *Blocking buffer*, and seal the bag. Incubate for 30 minutes with constant agitation. Open each bag, and pour out the *Blocking buffer*. Add 9 mL of the diluted *Primary antibody solution* against PA to the bag containing the strip marked PA. Similarly, add 9 mL of the diluted *Primary antibody solution* against LF and EF to the bags containing strips labeled LF and EF, respectively. Seal the bags, and incubate under agitation for 2 hours at room temperature or overnight at 2° to 8°. Remove the strips from the plastic bags, and place in separate plastic boxes. Add sufficient *Blocking buffer* so that each strip is completely immersed. Agitate for at least 30 minutes at room temperature with two changes of *Blocking buffer*. Remove the strips, and place each strip in a new heat-sealable plastic bag. Add 9 mL of the *Secondary antibody solution* to each plastic bag. Seal the bags, and incubate for 1 hour at room temperature under agitation. Remove the strips from the plastic bags, and place in separate plastic boxes. Add sufficient *Blocking buffer* so that each strip is completely immersed. Agitate for at least 30 minutes at room temperature with two changes of the *Blocking buffer*. Transfer each strip into a new heat-sealable plastic bag, add 9 mL *Chromogenic visualization solution*, 10 µL of 30% (v/v) hydrogen peroxide, and seal the bags. Incubate for about 30 minutes under agitation. Transfer the strips into separate plastic boxes, and remove the excess 4-chloro-1-naphthol by incubating with water under agitation for 10 minutes. Visual observation indicates a strong positive band on the strip labeled PA (Protective Antigen), a faintly detectable band on the strip labeled LF (Lethal Factor), and no detectable band on the strip labeled EF (Edema Factor).

83 kDa protein—

Trichloroacetic acid solution, Sample buffer, Running buffer, and *Test solution*—Prepare as directed under *Identification*.

Staining solution—Prepare a solution of Coomassie blue G-250 having a concentration of 1.25 g per L in a mixture of water, methanol, and acetic acid (5:4:1, v/v).

Protein molecular weight standard solution—Reconstitute a vial of protein molecular weight standard mixture containing proteins of molecular weights at least in the range of 14 to 200 kDa, according to manufacturer's instruction. Dilute the solution with *Sample buffer* such that the concentration of each protein in the solution is about 0.5 µg per µL.

Procedure—In a suitable centrifuge tube transfer 10/*c* mL of the *Test solution*, where *c* is the total protein concentration, in µg per mL, of the solution as determined by the test for *Total protein* (see below). Add 5.5/*c* mL of *Trichloroacetic acid solution*, and incubate for at least 10 minutes. Centrifuge at 9,000*g* for about 10 minutes, decant off the supernatant, and hold the tube inverted to drain on a filter paper. Dissolve the pellet in 20 µL of *Sample buffer*, and

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transfer the solution to a polypropylene microfuge tube with a lid. Transfer 20 µL of *Protein molecular weight standard solution* to another polypropylene microfuge tube with a lid. Close the lids tightly, secure with lid-locks, and heat both solutions at 100° for 5 minutes. Allow the solutions to cool to room temperature, and centrifuge at 10,000*g* for 15 seconds to collect the liquids. Apply the solutions to two consecutive lanes of a 4%–20% gradient tris-glycine polyacrylamide slab gel [NOTE—Do not apply any solution in the outside lanes.], and electrophorese as directed under *Identification* (see *Electrophoresis* ⟨726⟩ and the section *Polyacrylamide Gel Electrophoresis* under *Biotechnology-Derived Articles—Tests* ⟨1047⟩). When the dye-front is about 1 cm from the bottom of the gel (about 40 minutes), stop the current, and remove the gel from the gel assembly. Soak the gel in a suitable volume of the *Staining solution* for at least 1 hour, such that the gel is completely immersed in the *Staining solution* during staining. [NOTE—Do not touch the gel with bare hand. Use disposable gloves.] Destain the gel with a large volume of water under constant agitation with repeated changes of water until the background of the gel is completely color free. Using the molecular weights of the proteins in *Protein molecular weight standard solution*, identify the band corresponding to the Protective Antigen (MW about 83 kDa) in the *Test solution* lane. [NOTE—This band is also the single most predominant band in the lane of the *Test solution*.] Scan the gel, and determine the relative amount (by peak area) of the 83-kDa band by densitometry in the lane of the *Test solution*. The content of 83 kDa band is not less than 35% of the total peak area.

Total protein—

Standard solution A—Prepare a solution of albumin bovine serum (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) in water to obtain a known concentration of about 2.0 mg per mL.

Standard solutions B, C, D, and *E*—Dilute *Standard solution A* with water to obtain solutions having protein concentrations of 4, 8, 16, and 24 µg per mL, respectively.

Test solution—Use Anthrax Vaccine Filtrate as is.

Procedure (See *Biotechnology-Derived Articles—Tests* ⟨1047⟩, Total Protein Assay, Method 3)—To a series of test tubes transfer 800 µL each of *Standard solutions B, C, D,* and *E* and the *Test solution*. Also transfer 800 µL of water to be used as the blank. Add 200 µL of Coomassie blue G-250 dye solution (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) to each tube, and mix without foaming. Determine absorbances of the solutions at 595 nm using a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩), using the blank to set the instrument to zero. [NOTE—Do not use quartz (silica) spectrophotometer cells; the dye binds to silica.] Construct a standard curve by plotting the absorbances versus protein concentrations, in µg per mL, of *Standard solutions B, C, D,* and *E* and by drawing a best-fit straight line using the linear regression method. From the standard curve, determine the total protein concentration of the *Test solution* using the absorbance value. The protein concentration is between 5 and 20 µg per mL.

FINAL PRODUCT—

Aluminum—

Standard solutions—Prepare as directed for *Standard Preparations* under *Aluminum* ⟨206⟩, except to prepare solutions containing 10, 20, 30, 40, and 50 µg per mL of aluminum.

Test solution—Mix Anthrax Vaccine Adsorbed, Final Product well, and transfer 0.2 mL to a 10-mL volumetric flask. Add 0.5 mL of concentrated sulfuric acid and 0.5 mL of concentrated nitric acid, and mix gently. Incubate at room temperature for 30 minutes or until the solution becomes essentially clear. Dilute with water to volume.

Procedure—Proceed as directed for *Procedure* under *Aluminum* ⟨206⟩. Plot the absorbances versus the content of aluminum, in µg per mL, for the *Standard solutions*, and draw a best-fit straight line through the points using a linear regression model. Calculate the amount of aluminum in Anthrax Vaccine Adsorbed, in mg per mL. The aluminum concentration is between 0.8 and 1.5 mg per mL.

Safety—It meets the requirements when tested as directed in the section *Safety Tests—Biologicals* under *Biological Reactivity Tests, In Vivo* ⟨88⟩.

Sterility ⟨71⟩—It meets the requirements when tested as directed for *Direct Inoculation of the Culture Medium* method under *Test for Sterility of the Product to be Examined*.

pH ⟨791⟩: between 7.5 and 8.5.

Sodium chloride—

Standard solutions A and *B*—Prepare two solutions of sodium chloride in water having concentrations of 0.2 mM and 2.0 mM, respectively.

Test solution—Transfer 0.5 mL of Anthrax Vaccine Adsorbed, Final Product to a 50-mL volumetric flask. Dilute with water to volume.

Procedure—Determine the voltage readings of *Standard solutions A* and *B* and the *Test solution* using an ion-specific electrode specific for the chloride ion electrically coupled with a standard silver–silver chloride reference electrode. Plot the voltage readings versus concentration of chloride, in mg per mL, for *Standard solutions A* and *B*, and draw a straight line joining the points. Calculate the concentration of chloride ion in the *Test solution* from the voltage reading. Assuming that the chloride ion comes entirely from sodium chloride, calculate the concentrations of sodium chloride in the *Test solution*. The concentration of sodium chloride in Anthrax Vaccine Adsorbed is between 0.75% and 0.95% (w/v).

Formaldehyde—

Potassium ferricyanide solution—Dissolve 2.5 g of potassium ferricyanide in about 100 mL of water, and mix.

Phenylhydrazine hydrochloride solution—Dissolve 4 g of phenylhydrazine hydrochloride in 100 mL of absolute alcohol, add 2 mL of water, and mix.

Standard stock solution—To prepare a stock solution, proceed as directed in the *Assay* under *Formaldehyde Solution* to determine the concentration of formaldehyde in percent (w/v).

Standard solutions—Dilute the *Standard stock solution* in water to obtain solutions having concentrations of 0.005%, 0.01%, and 0.02% (w/v).

Test solution—Use Anthrax Vaccine Adsorbed, Final Product as is.

Procedure—To suitable glass centrifuge tubes transfer 1.0 mL each of water, the *Standard solutions*, and the *Test solution*. To each tube add 1.0 mL of *Potassium ferricyanide solution*, 4.0 mL of 18% (w/v) hydrochloric acid and 2.0 mL of *Phenylhydrazine hydrochloride solution*. Mix after each addition. Incubate for 50 to 60 minutes at room temperature. Centrifuge the solutions at 10,000*g* for at least 10 minutes, and measure absorbances of the supernatants at 540 nm using a suitable spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩). Plot the absorbances versus concentrations of formaldehyde, in mg per mL, in the *Standard solutions*, and draw the best-fit straight line through the points. Calculate the amount of formaldehyde in the sample in percent (w/v). The concentration of formaldehyde in Anthrax Vaccine Adsorbed is less than 0.02% (w/v).

Benzethonium chloride—

Citrate buffer—Dissolve 25 g of citric acid monohydrate in about 60 mL of water, and adjust with a solution of sodium hydroxide to a pH of 4.5. Transfer the solution to a 100-mL volumetric flask. Dilute with water to volume, and mix.

Dye solution—Dissolve 50 mg of 2′,4′,5′,7′-tetrabromofluorescein in about 100 mL water, and mix. Dilute 1 mL of this solution to 100 mL with water.

Docusate sodium solution—Dissolve 50 mg of docusate sodium in 1 L of water.

Standard solution A—Transfer about 0.5 g, accurately weighed, of benzethonium chloride to a 100-mL volumetric flask, dissolve in about 60 mL water, dilute with water to volume, and mix.

Standard solutions B, C, D, and *E*—Dilute *Standard solution A* with water to obtain solutions having concentrations of 0.001%, 0.002%, 0.003%, and 0.004% (w/v), respectively.

Test solution—Use Anthrax Vaccine Adsorbed, Final Product as is.

Procedure—Transfer 4.0 mL each of *Standard solutions B, C, D,* and *E* and the *Test solution* to suitable glass centrifuge tubes. Add 1.0 mL *Citrate buffer* and 0.4 mL of the *Dye solution* to each tube, and mix. Add 4.0 mL of 1,1,2,2-tetrachloroethane to each tube, and vigorously mix on a vortex mixer for 1 minute. Centrifuge at about 1,000*g* for at least 15 minutes to separate the organic layer from the aqueous layer. Transfer 2.0 mL of the organic layer from the tubes to another set of glass tubes. Add 4.0 mL of water and 0.5 mL of *Citrate buffer* to each tube, and mix on a vortex mixer for approximately 1 minute. Titrate the benzethonium chloride-dye complex in each tube with the *Docusate sodium solution* (see *Titrimetry* ⟨541⟩) to the colorimetric endpoint indicated by the disappearance of the pink color of the organic layer. [NOTE—Vigorously mix the solution on a vortex mixer after each addition of the *Docusate sodium solution*.] Plot the volumes of *Docusate sodium solution* required versus the concentrations of benzethonium chloride in *Standard solutions B, C, D,* and *E*, and draw a best-fit straight line through the points. Determine the concentration of benzethonium chloride in the *Test solution* from the volume of *Docusate sodium solution* required to titrate the *Test solution*. The concentration of benzethonium chloride in Anthrax Vaccine Adsorbed is between 0.0015% and 0.0030% (w/v).

Relative potency—

Standard solutions—Dilute approved U.S. Reference Standard Anthrax Vaccine 1:1.6, 1:4, 1:10, and 1:25 aseptically with a sterile 0.9% sodium chloride solution.

Test solutions—Dilute Anthrax Vaccine Adsorbed, Final Product 1:1.6, 1:4, 1:10, and 1:25 aseptically with a sterile 0.9% sodium chloride solution.

Procedure—Assign each dilution to a set of 12 randomly selected guinea pigs, strain Mdh:S(RA), 6 males and 6 females, each weighing 315 to 385 g on the day of vaccination. Inject the animals subcutaneously in the ventral abdomen with 0.5 mL of the assigned dilutions. On the 14th day post-vaccination, challenge the animals with approximately 1000 spores of *Bacillus anthracis* Vollum 1B, and record the deaths daily for a 10-day observation period. Record the numbers of surviving animals for each of the *Standard solutions* and the *Test solutions* at the end of the test. Perform calculations by estimating best-fit lines for the *Standard solutions* and the *Test solutions* using a logistic regression model that utilizes the number of animals that survived at the end of the test and the time to death for the animals that died. Evaluate statistically the lines corresponding to the *Standard solutions* and the *Test solutions* for parallelism. Determine the common slope, and draw the parallel lines using the common slope. The relative potency

of Anthrax Vaccine Adsorbed with respect to the corresponding Approved U.S. Reference Standard Anthrax Vaccine is the antilog of the horizontal distance between the two parallel lines. The relative potency of Anthrax Vaccine Adsorbed is acceptable if it is between 0.53 and 1.79, both values inclusive.■1S (*USP27*)

BRIEFING

Atracurium Besylate Injection, page 2943 of the *First Supplement* and page 593 of the *Third Interim Revision Announcement* to *USP 26* and *NF 21* of *PF* 29(3) [May–June 2003].The limit for other known impurities in the test for *Related compounds* is proposed to be modified to reflect the levels found in approved products.

(PA3: S. Salado) RTS—39720-1

Change to read:

Related compounds—

Buffer solution, *Solution A*, *Solution B*, *Mobile phase*, and *Standard preparation*—Proceed as directed in the *Assay* under *Atracurium Besylate.*

System suitability solution—Heat a portion of the *Standard preparation* at 90° for 30 minutes, and chill immediately to about 5°.

Diluted standard preparation—Dilute a portion of the *Standard preparation* quantitatively, and stepwise if necessary, with *Solution A* to obtain a solution having a known concentration of about 0.02 mg per mL.

Test preparation—Use the *Assay preparation*.

Chromatographic system—Prepare as directed for *Chromatographic system* in the *Assay.* Chromatograph the *System suitability solution* and the *Diluted standard preparation*, record the chromatograms, and measure the responses for the degradation products by comparing the peak responses of the *System suitability solution* to those of the *Diluted standard preparation* as directed for *Procedure:* the retention times relative to the atracurium besylate *cis-cis*-isomer are about 0.22 for the acidic compound, 0.29 for laudanosine, 0.44 and 0.50 for the *trans*- and *cis*-isomers, respectively, of the hydroxy compound, and about 1.28 and 1.33 for the *trans*- and *cis*-isomers, respectively, of the monoacrylate.

Procedure—Separately inject equal volumes (about 20 µL) of the *Diluted standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the peak responses, except the peak due to benzenesulfonic acid occurring at a retention time of about 0.08 relative to the atracurium besylate *cis-cis*-isomer. Calculate the percentage of each impurity in the portion of *Test preparation* taken by the formula:

$$100(C/M)(r_i / r_s),$$

in which C is the concentration, in mg per mL, of USP Atracurium Besylate RS in the *Diluted standard preparation; M* is the concentration of atracurium besylate, in mg per mL, in the *Test preparation; r_i* is the peak response for each impurity obtained from the *Test preparation;* and r_s is the sum of the responses of all the peaks obtained from the *Diluted standard preparation:* not more than 6.0% of the acidic compound, not more than 6.0% of the combined *cis*- and *trans*-isomers of the hydroxy compound, not more than 3.0% of laudanosine, and not more than 3.0% of the combined *cis*- and *trans*-isomers of the monoacrylate, ●~~and not more than 0.5% of other known impurities~~●,

■and not more than 2.0% of other known impurities■1S (*USP27*)
is found; not more than 0.1% of any other impurity is found; and not more than 15.0% of total impurities is found.

●~~(Postponed Indefinitely)~~●.

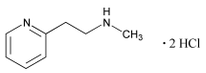
BRIEFING

Betahistine Hydrochloride, page 1401 of *PF* 26(5) [Sept.–Oct. 2000]. This new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision* with editorial changes. Based on the comments received it is proposed to replace alcohol with absolute alcohol as a *Diluent* in *Related compounds* section.

(PA5: A. Wilk) RTS—39859-1

Add the following:

■Betahistine Hydrochloride



$C_8H_{12}N_2 \cdot 2HCl$ 209.12

2-Pyridineethanamine, *N*-methyl-, dihydrochloride.

2-[2-(Methylamino)ethyl]pyridine dihydrochloride [*5579-84-0*].

» Betahistine Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $C_8H_{12}N_2 \cdot 2HCl$, calculated on the dried basis.

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Packaging and storage—Preserve in well-closed, light-resistant containers.

USP Reference standards ⟨11⟩—*USP Betahistine Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The R_F value and intensity of the principal spot in the chromatogram of *Test solution 2* correspond to those in the chromatogram of *Standard solution 1*, obtained as directed in the test for *Related compounds.*

pH ⟨791⟩: between 2.0 and 3.0, in a solution (1 in 10).

Loss on drying ⟨731⟩—Dry it between 100° and 105° to constant weight: it loses not more than ~~0.5%~~ 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Related compounds—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Diluent—Prepare a mixture of alcohol and water (3:1).

Test solution 1—Dissolve about 250 mg of Betahistine Hydrochloride, accurately weighed, in 5.0 mL of *Diluent.*

Test solution 2—Dilute 1.0 mL of *Test solution 1* with *Diluent* to 25.0 mL, and mix.

Resolution solution—Pepare a solution of USP Betahistine Hydrochloride RS and 2-vinylpyridine in *Diluent* containing 1.0 mg of each per mL.

Standard solution 1—Prepare a solution of USP Betahistine Hydrochloride RS in *Diluent* containing 2.0 mg per mL.

Standard solution 2—Dilute 1.0 mL of *Standard solution 1* with *Diluent* to 20.0 mL. Dilute 1.0 mL of this solution with *Diluent* to 20.0 mL, and mix.

~~*Standard solution 3*—Dilute 5.0 mL of *Standard solution 2* with *Diluent* to 5.0 mL, and mix.~~

Application volume: 5 µL.

Developing solvent system: a mixture of toluene, absolute alcohol, and ammonium hydroxide (10:5:1).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩, except to ~~develop~~ dry the plate under a current of warm air, in a hood, ~~and then dry~~ followed by heating for 10 minutes at 110°. Examine the plate under short-wavelength UV light using a quantitative scanner. The resolution, *R*, between the peaks due to 2-vinylpyridine and betahistine in the scan of the chromatogram of the *Resolution solution* is not less than 3.0. The area obtained for any individual impurity is not greater than that obtained for the major peak in the chromatogram of *Standard solution 2:* not more than 0.25% of any individual impurity is found. The total amount of impurities found is not greater than twice the area of the major peak in the same solution: not more than 0.5% of total impurities is found.

Assay—Dissolve about 80 mg of Betahistine Hydrochloride, accurately weighed, in 60 mL of a mixture of glacial acetic acid and acetic anhydride (5:1). Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically, using suitable electrodes (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 10.455 mg of $C_8H_{12}N_2 \cdot 2HCl$.■1S (*USP27*)

BRIEFING

Betamethasone Oral Solution, *USP 26* page 233; **Betamethasone Syrup,** *USP 26* page 233; **Betamethasone Tablets,** *USP 26* page 234. It is proposed to revise the *Identification* test in accordance with the general chapter *Thin-Layer Chromatographic Identification Test* ⟨201⟩. It is also proposed to revise the *Packaging*

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and storage section to include the recommended temperature range, as established by the USP Packaging, Storage, and Distribution Expert Committee.

(PA1: C. Anthony; PSD: C. Okeke) RTS—39938-1

Betamethasone Oral Solution

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

Change to read:

Packaging and storage— ~~Preserve in well-closed containers.~~

■Store between 2° and 25°C, excursion permitted between 15° and 30°C, protected from light. Preserve in a tight container. Protect from freezing.■1S (*USP27*)

Delete the following:

■~~**Identification**— Evaporate 25 mL of the *Assay preparation*, prepared as directed in the *Assay*, on a steam bath just to dryness, and dissolve the residue in 0.5 mL of alcohol. Proceed as directed for *Identification* test *B* under *Betamethasone*, beginning with "Apply 10 µL of this solution."~~■1S (*USP27*)

Add the following:

■**Thin-Layer Chromatographic Identification Test** ⟨201⟩—

Test solution—Evaporate 25 mL of the *Assay preparation*, prepared as directed in the *Assay*, on a steam bath just to dryness, and dissolve the residue in 0.5 mL of alcohol.

Developing solvent system: a mixture of chloroform and diethylamine (2:1).

Procedure—Proceed as directed in the chapter. Locate the spots by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear.■1S (*USP27*)

BRIEFING

Betamethasone Syrup, *USP 26* page 233—See briefing under *Betamethasone Oral Solution*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—39938-1

Betamethasone Syrup

(Current title—not to change until June 1, 2005)
Monograph title change—to become official June 1, 2005
See **Betamethasone Oral Solution**

Change to read:

Packaging and storage— ~~Preserve in well-closed containers.~~

■Store between 2° and 25°C, excursion permitted between 15° and 30°C, protected from light. Preserve in a tight container. Protect from freezing.■1S (*USP27*)

Delete the following:

■~~**Identification**— Evaporate 25 mL of the *Assay preparation*, prepared as directed in the *Assay*, on a steam bath just to dryness, and dissolve the residue in 0.5 mL of alcohol. Proceed as directed for *Identification* test *B* under *Betamethasone*, beginning with "Apply 10 µL of this solution."~~■1S (*USP27*)

Add the following:

■**Thin-Layer Chromatographic Identification Test** ⟨201⟩—

Test solution—Evaporate 25 mL of the *Assay preparation*, prepared as directed in the *Assay*, on a steam bath just to dryness, and dissolve the residue in 0.5 mL of alcohol.

Developing solvent system: a mixture of chloroform and diethylamine (2:1).

Procedure—Proceed as directed in the chapter. Locate the spots by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear.■1S (*USP27*)

In-Process Revision

BRIEFING

Betamethasone Tablets, *USP 26* page 234—See briefing under *Betamethasone Oral Solution*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—39938-2

Change to read:

Packaging and storage— ~~Preserve in well-closed containers.~~

■Store between 2° and 25°C, excursion permitted between 15° and 30°C, and preserve in a tight container. [NOTE—Protect the 21-tablet pack from excessive moisture.]■1S (*USP27*)

Delete the following:

■~~**Identification**— Evaporate 50 mL of the *Assay preparation*, prepared as directed in the *Assay*, on a steam bath just to dryness, and dissolve the residue in 1 mL of chloroform. Proceed as directed for *Identification* test *B* under *Betamethasone*, beginning with "Apply 10 µL of this solution."~~■1S (*USP27*)

Add the following:

■**Thin-Layer Chromatographic Identification Test** ⟨201⟩—

Test solution—Evaporate 50 mL of the *Assay preparation*, prepared as directed in the *Assay*, on a steam bath just to dryness, and dissolve the residue in 1 mL of chloroform.

Developing solvent system: a mixture of chloroform and diethylamine (2:1).

Procedure—Proceed as directed in the chapter. Locate the spots on the plate by lightly spraying with dilute sulfuric acid (1 in 2) and heating on a hot plate or under a lamp until spots appear.■1S (*USP27*)

BRIEFING

Bleomycin for Injection, *USP 26* page 258. It is proposed to replace the *Loss on drying* test with a *Water* determination using *Method Ic* (coulometric titration). The hygroscopic nature of Bleomycin Sulfate causes considerable variation, as well as a high bias, in *Loss on drying* values. In addition, the lyophilized product is electrostatic and the powder is difficult to handle in sample preparation. It is therefore proposed to use a *Water* determination in which the sample is prepared by adding anhydrous methanol through the stopper of the container, and then titrating the constituted solution by *Method Ic.* USP has received data showing that this *Water* determination yielded less variable results than the *Loss on drying* procedure. The *Water* determination also yielded lower results. The results were in good agreement with water values obtained by thermal gravimetric analysis.

(PA7: W. Wright) RTS—39784-1

Delete the following:

■~~**Loss on drying** ⟨731⟩— Dry the total contents of 2 containers in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours: it loses not more than 6.0% of its weight.~~■1S (*USP27*)

Add the following:

■**Water,** *Method Ic* ⟨921⟩: not more than 6.0%. Prepare the specimen for test as follows. Use a dry syringe to inject 4 mL of anhydrous methanol through the stoppers of two tared containers, respectively, and shake to dissolve. Using the same syringe, aspirate the contents of the two containers, transfer to the titration vessel, and titrate. Perform a blank determination on 8 mL of the anhydrous methanol. Determine the weights of the empty containers, and calculate the percentage of water.■1S (*USP27*)

BRIEFING

Bupropion Hydrochloride, *USP 26* page 279. In the *Chromatography purity Test 1*, it is proposed to specify the wavelength for the densitometer used to scan the plates.

(PA3: S. Salado) RTS—39777-2

Change to read:

Chromatographic purity—

TEST 1—

Adsorbent: a 0.25-mm layer of high-performance silica gel, previously washed with methanol.

Test solution—Prepare a solution of Bupropion Hydrochloride in methanol having a concentration of about 100.0 mg per mL.

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Standard solutions—Prepare a solution of *m*-chlorobenzoic acid in methanol containing about 0.5 mg per mL. Dilute this solution quantitatively, and stepwise if necessary, with methanol to obtain solutions having known concentrations of about 0.3, 0.2, and 0.1 mg per mL.

Application volume: 2 µL.

Developing solvent system: a mixture of toluene, cyclohexane, and glacial acetic acid (47:47:6).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Locate and quantitate the spots obtained by scanning the entire plate with a suitable densitometer

■at 254 nm.■1S (*USP27*)
Plot a standard curve of area versus concentrations of the *Standard solutions.* From the standard curve, determine the percentages of *m*-chlorobenzoic acid and any other impurity present: not more than 0.2% of *m*-chlorobenzoic acid is found; and not more than 0.1% of any other individual impurity is found.

TEST 2—

Procedure—Using the chromatograms obtained in the *Assay*, calculate the percentage of each impurity in the portion of Bupropion Hydrochloride taken by the formula:

$$100F(r_i/r_S),$$

in which F is the relative response factor for each impurity (see the accompanying table for values); r_i is the peak response for each impurity obtained from the *Assay preparation;* and r_S is the peak response for bupropion hydrochloride obtained from the *Standard preparation*. The limits of impurities are specified in the accompanying table: not more than 0.3% of total unidentified impurities is found; and not more than 1.0% of total impurities is found, the results of *Test 1* and *Test 2* being added.

Relative retention time	Relative response factor (*F*)	Limit (%)
0.38	0.68	0.5
0.58	0.96	0.2
0.71	2.22	0.1
0.78	0.82	0.1
0.92	0.73	0.2
1.14	n/a	0.2[a]
1.63	1.13	0.1
2.30	0.91	0.2
2.74	1.45	0.2
all other peaks[b]	1.00	0.1

[a] The percentage is determined by direct comparison to the area of the peak for bupropion hydrochloride related compound B obtained from the *System suitability solution.*

[b] Except the peaks with relative retention time of 1.14.

BRIEFING

Bupropion Hydrochloride Extended-Release Tablets, *USP 26* page 280 and page 1074 of *PF* 28(4) [July–Aug. 2002]. In the *Assay*, it is proposed to revise the concentration of bupropion hydrochloride specified for making up the *Assay preparation.*

(PA3: S. Salado) RTS—39777-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Crush 1 Tablet using a mortar and pestle. Prepare an approximate 1% w/w dispersion of the sample in potassium bromide:

■the *Test specimen* shows strong bands at about 1690, 1560, and 1240 cm^{-1} and a weaker band at about 790 cm^{-1} similar to the reference preparation.■1S (*USP27*)

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

Change to read:

Related compounds—

Solution A, *Solution B*, *Mobile phase*,

■*System suitability solution 1*, and *System suitability solution 2*■1S (*USP27*)
—Proceed as directed in the *Assay.*

~~*System suitability solution*—Prepare separate solutions containing accurately weighed amounts of USP Bupropion Hydrochloride Related Compound C RS and USP Bupropion Hydrochloride Related Compound F RS in methanol to obtain solutions having concentrations of about 0.20 mg per mL. Transfer accurately measured volumes of these solutions to a suitable flask, and dilute with a mixture of 0.001 N hydrochloric acid and methanol (80:20) to obtain a solution having a concentration of about 0.0018 mg of USP Bupropion Hydrochloride Related Compound C RS per mL and 0.018 mg of USP Bupropion Hydrochloride Related Compound F RS per mL.~~

~~*Wavelength check solution*—Prepare a solution containing an accurately weighed amount of *m*-chlorobenzoic acid in methanol to obtain a solution having a concentration of about 0.09 mg per mL. Dilute an accurately measured volume of this solution with a mixture of 0.001 N hydrochloric acid and methanol (80:20) to obtain a solution having a concentration of about 0.0018 mg of *m*-chlorobenzoic acid per mL.~~

■■1S (*USP27*)

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Standard solution—Dissolve accurately weighed quantities of USP Bupropion Hydrochloride RS and USP Bupropion Hydrochloride Related Compound E RS in a mixture of 0.001 N hydrochloric acid and methanol (80:20) to obtain a solution having known concentrations of about 0.6 mg per mL and 0.0024 mg per mL, respectively.

Test solution—Use the *Assay preparation.*

Chromatographic system—~~Prepare~~

■Proceed■1S (*USP27*) as directed in the *Assay*, ~~Chromatograph the *System suitability solution*, the *Wavelength check solution*, and the *Standard solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between bupropion hydrochloride related compound C and bupropion hydrochloride related compound F is not less than 1.5; and the relative standard deviation for replicate injections is not more than 1.5%. The relative response factor obtained for the *Wavelength check solution* is between 0.22 and 0.26.~~

■except to use the *Standard solution* instead of the *Standard preparation*.■1S (*USP27*)

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of bupropion hydrochloride related compound E in the portion of Tablets taken by the formula:

$$100(C/D)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Bupropion Hydrochloride Related Compound E RS in the *Standard solution;* D is the concentration, in mg per mL, of bupropion hydrochloride in the *Test solution*, based on the number of Tablets taken, the labeled quantity per Tablet, and the extent of dilution; and r_U and r_S are the peak responses for bupropion hydrochloride related compound E obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.4% of bupropion hydrochloride related compound E is found. Calculate the percentage of each additional impurity in the portion of Tablets taken by the formula:

$$100F(r_i/r_S),$$

in which F is the relative response factor for each impurity (see the accompanying table for values); r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for bupropion hydrochloride obtained from the *Standard solution*. See the accompanying table for limits of individual impurities based upon Tablet strength.

Compound	Relative Retention Time	*F*	Limit (%) 100 mg or less	Limit (%) 150 mg or greater
Specified impurity 1	0.38	0.80	0.3	0.3
Specified impurity 2	0.56	0.86	1.0	1.0
Specified impurity 3	0.78	0.88	0.5	0.4
Bupropion related compound F	1.71	0.55	1.2	2.3
Bupropion related compound C	1.75	0.59	0.3	0.3
m-Chlorobenzoic acid	1.80	0.24	0.3	0.3
Bupropion related compound E	2.25	1.00	0.4	0.4
Any unspecified impurity	—	1.00	0.2	0.2
Total impurities	—	—	3.2	3.3

Change to read:

Assay—

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (90:10:0.04).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, water, and trifluoroacetic acid (95:5:0.03).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

■*System suitability solution 1*—Prepare separate solutions containing accurately weighed quantities of USP Bupropion Hydrochloride Related Compound C RS and USP Bupropion Hydrochloride Related Compound F RS in methanol to obtain solutions having concentrations of about 0.20 mg per mL. Transfer accurately measured volumes of these solutions to a suitable flask, and dilute with a mixture of 0.001 N hydrochloric acid and methanol (80:20) to obtain a solution having a concentration of about 0.0018 mg of USP Bupropion Hydrochloride Related Compound C RS per mL and 0.018 mg of USP Bupropion Hydrochloride Related Compound F RS per mL.

System suitability solution 2—Prepare a solution containing an accurately weighed quantity of *m*-chlorobenzoic acid to obtain a solution having a concentration of about 0.09 mg per mL. Dilute an accurately measured volume of this solution with a mixture of 0.001 N hydrochloric acid and methanol (80:20) to obtain a solution having a concentration of about 0.0018 mg of *m*-chlorobenzoic acid per mL.■1S (*USP27*)

Standard preparation—Dissolve an accurately weighed quantity of USP Bupropion Hydrochloride RS in a mixture of 0.001 N hydrochloric acid and methanol (80:20) to obtain a solution having a known concentration of about 0.6 mg of bupropion hydrochloride per mL.

Assay preparation—Transfer a number of Tablets to a suitable homogenizer vessel containing an accurately measured volume of methanol to obtain a concentration of about ~~0.3 mg~~

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■3.0 mg■1S (*USP27*) of bupropion hydrochloride per mL. Immediately homogenize the sample for 30 seconds at 20,000 rpm. Allow to extract for 3 minutes, and follow by two additional 10-second pulses, each at 20,000 rpm, pausing 3 minutes between these pulses to ensure complete extraction. Pass a portion of the solution through a nylon filter having a 0.45-µm porosity, discarding the first 2 to 4 mL of the filtrate. Pipet 10.0 mL of the filtrate into a 50-mL volumetric flask, and add about 25 mL of 0.001 N hydrochloric acid. Allow to cool to room temperature, and dilute with 0.001 N hydrochloric acid to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 226-nm detector and a 4.6-mm × 10-cm column that contains 3.5-µm packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	90	10	equilibration
0–3.4	90→87	10→13	linear gradient
3.4–10.0	87→15	13→85	linear gradient
10.0–10.1	15→0	85→100	linear gradient
10.1–13.0	0	100	isocratic
13.0–13.2	0→90	100→10	linear gradient
13.2–19.0	90	10	isocratic

~~Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 1.5%.~~

■Chromatograph *System suitability solution 1*, *System suitability solution 2*, and the *Standard preparation*, and record the peak areas as directed for *Procedure:* the resolution, *R*, between bupropion hydrochloride related compound C and bupropion hydrochloride related compound F is not less than 1.5; the relative response factor for *System suitability solution 2* is between 0.22 and 0.26 when calculated using the peak obtained in the *Standard preparation*; the tailing factor is not more than 1.9; and the relative standard deviation for replicate injections of the *Standard preparation* is not more than 1.5%.■1S (*USP27*)

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the amount, in mg, of buproprion hydrochloride ($C_{13}H_{18}ClNO \cdot HCl$) in the portion of Tablets taken by the formula:

$$(TC/D)(r_U/r_S),$$

in which T is the labeled quantity, in mg, of bupropion hydrochloride in the Tablet; *C* is the concentration, in mg per mL, of USP Bupropion Hydrochloride RS in the *Standard preparation; D* is the concentration, in mg per mL, of bupropion hydrochloride in the *Assay preparation*, based upon the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the peak responses for bupropion hydrochloride obtained from the *Assay preparation* and the *Standard preparation*, respectively.

BRIEFING

Cefuroxime Axetil Tablets, *USP 26* page 389. The proposal on page 2128 of *PF* 27(2) [Mar.–Apr. 2001] for *Test 2* under *Dissolution* is being cancelled. A new *Test 2* is being proposed because FDA recently approved an ANDA for this product. Because of differences in dissolution rates in vitro, the new product was approved with a *Dissolution* test that differs from that currently official in the *USP* monograph. In the absence of any adverse comments, it is proposed to implement this revision via the *Sixth Interim Revision Announcement* pertaining to *USP 26–NF 21* with an official date of December 1, 2003.

(BPC: M. Marques) RTS—39544-1

Change to read:

Labeling—The labeling indicates whether the Tablets contain amorphous or crystalline Cefuroxime Axetil. If Tablets contain a mixture of amorphous and crystalline Cefuroxime Axetil, label to indicate the percentage of each contained therein.

•When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.•6

Change to read:

Dissolution ⟨711⟩—

•*Test 1:*•6
Medium: 0.07 N hydrochloric acid; 900 mL.
Apparatus 2: 55 rpm.
Times: 15 and 45 minutes.
Procedure—Determine the amount of cefuroxime ($C_{16}H_{16}N_4O_8S$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about 278 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Cefuroxime Axetil RS, equivalent to about 0.01 to 0.02 mg of cefuroxime ($C_{16}H_{16}N_4O_8S$) per mL, in the same *Medium.*
Tolerances—Not less than 60% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 15 minutes, and not less than 75% (*Q*) is dissolved in 45 minutes; except that where Tablets are labeled to contain the equivalent of 500 mg of cefuroxime, not less than 50% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 15 minutes, and not less than 70% (*Q*) is dissolved in 45 minutes.

•*Test 2:* If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Apparatus 2: 100 rpm.

Medium, Times, and *Procedure*—Proceed as directed under *Test 1*.

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Tolerances—Not less than 60% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 15 minutes, and not less than 75% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 45 minutes.●6

BRIEFING

Ciclopirox Olamine, *USP 26* page 451 and page 395 of *PF* 29(2) [Mar.–Apr. 2003]. It is proposed to delete the *Loss on drying* test due to the difficulty of performing the test for this substance. The acceptance criteria for the *Assay* result are therefore modified to as-is basis. Additionally, the packaging requirement was modified to minimize the exposure to moisture.

(PA7b: B. Davani) RTS—39957-1

Change to read:

» Ciclopirox Olamine contains not less than ~~98.0~~

■97.5■1S (*USP27*)
percent and not more than ~~102.0~~

■101.5■1S (*USP27*)
percent of ciclopirox olamine ($C_{12}H_{17}NO_2 \cdot C_2H_7NO$). ~~calculated on the dried basis.~~

■■1S (*USP27*)

Change to read:

Packaging and storage—Preserve in ~~well-closed~~

■tight■1S (*USP27*)
containers

▲protected from light. Store between ~~15°~~ ■5°■1S (*USP27*) and ~~30°~~■25°.■1S (*USP27*) ▲*USP27*

Change to read:

USP Reference standards ⟨11⟩—*USP Ciclopirox Olamine RS.*

▲*USP Ciclopirox Related Compound A RS. USP Ciclopirox Related Compound B RS.*▲*USP27*

Change to read:

Identification—

~~**A:**~~

■■1S (*USP27*)

Infrared Absorption ⟨197K⟩.

~~**B:** Prepare a test solution by dissolving a suitable quantity of it in methanol to obtain a concentration of about 40 mg per mL. Similarly prepare a Standard solution, using USP Ciclopirox Olamine RS. Separately apply 10-µL portions of the test solution and the Standard solution to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of octadecylsilanized chromatographic silica gel mixture, and allow the spots to dry. Place the plate in a suitable chromatographic chamber saturated with a solvent system consisting of a mixture of acetonitrile, isopropyl alcohol, water, 1 M methanolic tetrabutylammonium hydroxide, and glacial acetic acid (50:40:10:0.8:0.6), and develop the chromatogram with the same solvent system. When the solvent front has moved about three-fourths of the length of the plate, remove the plate from the chamber, and allow to dry. Expose the plate to iodine vapors for 3 hours, and locate the spots on the plate: the R_f values of the principal spots obtained from the test solution correspond to those obtained from the Standard solution.~~

▲▲*USP27*

Change to read:

pH ⟨791⟩: between 8.0 and 9.0, ~~in a solution (1 in 100).~~

▲in a mixture with water (1:100).▲*USP27*

Delete the following:

■~~**Loss on drying** ⟨731⟩—Dry it in vacuum to constant weight: it loses not more than 1.5% of its weight.~~■1S (*USP27*)

Change to read:

Heavy metals, *Method II* ⟨231⟩: not more than ~~0.002%.~~

▲0.001%.▲*USP27*

Change to read:

Monoethanolamine content—Dissolve about 300 mg, accurately weighed, in 25 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 6.108 mg of C_2H_7NO. The content of monoethanolamine (C_2H_7NO)~~, calculated on the dried basis,~~

■■1S (*USP27*)
is not less than 223 mg and not more than 230 mg per g of $C_{12}H_{17}NO_2 \cdot C_2H_7NO$ found in the *Assay.*

Add the following:

▲**Related compounds**—[NOTE—Carry out the operations avoiding exposure to actinic light. All materials that are in direct contact with Ciclopirox Olamine (i.e, column materials, reagents, solvents, etc.) should contain only very low amounts of extractable metal cations.]

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Mobile phase—Prepare a filtered and degassed mixture of an edetate disodium solution (0.96 in 1000), acetonitrile, and glacial acetic acid (770:230:0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Rinsing solution—Prepare a mixture of water, acetonitrile, glacial acetic acid, and acetylacetone (500:500:1:1).

Standard stock solution—Dissolve 15 mg of USP Ciclopirox Related Compound A RS and 15 mg of USP Ciclopirox Related Compound B RS, accurately weighed, in 1 mL of acetonitrile and 7 mL of *Mobile phase*. Dilute the solution thus obtained to 10.0 mL with *Mobile phase* to obtain a solution having a known concentration of 1.5 mg of each Reference Standard per mL.

Standard solutions—Dilute 1.0 mL of *Standard stock solution* to 200.0 mL with a mixture of *Mobile phase* and acetonitrile (9:1) to obtain *Standard solution A.* Dilute 2.0 mL of *Standard solution A* to 10.0 mL with a mixture of *Mobile phase* and acetonitrile (9:1) to obtain *Standard solution B.*

Test solution—Dissolve 40 mg of Ciclopirox Olamine, accurately weighed, in a mixture of 2 mL of acetonitrile, 20 µL of glacial acetic acid, and 15 mL of *Mobile phase*. If necessary, use an ultrasonic bath to dissolve. Dilute with *Mobile phase* to 20.0 mL, and mix.

Resolution solution—Mix 5 mL of *Standard stock solution* with 5 mL of the *Test solution.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a detector capable of recording at both 220 nm and 298 nm and a 4.0-mm × 8-cm column that contains packaging L10. [NOTE—ciclopirox related compound A has an intense absorbance at 220 nm and 6-cyclohexyl-4-methyl-2(1*H*)-pyridone, ciclopirox related compound B, and ciclopirox have intense absorbances at 298 nm.] The flow rate is about 0.7 mL per minute. Chromatograph the *Resolution solution* at 298 nm, and record the peak responses as directed for *Procedure:* the resolution between the ciclopirox related compound B peak and ciclopirox peak is not less than 2.0. Chromatograph the *Standard solution B* at 298 nm, and record the peak responses as directed for *Procedure:* the chromatogram obtained shows at 298 nm a peak corresponding to ciclopirox related compound B with a signal-to-noise ratio of not less than 3. Chromatograph the *Test solution* at 298 nm, and record the peak responses as directed for *Procedure:* the tailing factor of the ciclopirox peak is less than 2.0.

Procedure—Separately inject equal volumes (about 10 µL) of *Standard solutions A* and *B* and the *Test solution* into the chromatograph, and record the chromatograms. [NOTE—In order to ensure desorption of disruptive metal ions, every new column must be rinsed with the *Rinsing solution* over a period of not less than 15 hours and then with the *Mobile phase* for not less than 5 hours with a flow rate of 0.2 mL per minute. The chromatographic run time is not less than 2.5 times the retention time of the ciclopirox peak.] The relative retention times are about 0.5 for ciclopirox related compound A, 0.9 for 6-cyclohexyl-4-methyl-2(1*H*)-pyridone, 1.0 for ciclopirox, and 1.3 for ciclopirox related compound B. The peak response at 220 nm of the ciclopirox related compound A peak in the chromatogram obtained from the *Test solution* is not more than the peak response at 220 nm of the corresponding peak in the chromatogram obtained from *Standard solution A* (0.5% with reference to ciclopirox). The sum of responses at 298 nm of the peaks in the chromatogram obtained from the *Test solution* is not more than the peak response at 298 nm of the ciclopirox related compound B peak in the chromatogram obtained from *Standard solution A* (0.5% with reference to ciclopirox). At 298 nm disregard any peak due to the solvent and any peak with a response less than the response

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of the ciclopirox related compound B peak in the chromatogram obtained from *Standard solution B* at 298 nm (0.1% with reference to ciclopirox).▲*USP27*

Change to read:

Assay—

~~*Ferrous sulfate solution*—Transfer 600 mg of ferrous sulfate to a 25-mL volumetric flask. Add 0.6 mL of glacial acetic acid, dilute with water to volume, and mix.~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Ciclopirox Olamine RS in methanol to obtain a solution having a known concentration of about 0.4 mg per mL.~~

~~*Assay preparation*—Transfer about 40 mg of Ciclopirox Olamine, accurately weighed, to a 100-mL volumetric flask, dissolve in about 80 mL of methanol, dilute with methanol to volume, and mix.~~

~~*Procedure*—Transfer 5.0 mL of the *Standard preparation*, 5.0 mL of the *Assay preparation*, and 5.0 mL of methanol (blank preparation) to separate 25-mL volumetric flasks. Add 15 mL of methanol to each flask, and mix. Add 1.0 mL of *Ferrous sulfate solution* to each flask, mix, dilute with methanol to volume, and mix. Store the flasks in the dark for 1 hour. Concomitantly determine the absorbances of the solutions from the *Assay preparation* and the *Standard preparation* against the blank in 1-cm cells at the wavelength of maximum absorbance at about 440 nm, with a suitable spectrophotometer. Calculate the quantity, in mg, of $C_{12}H_{17}NO_2 \cdot C_2H_7NO$ in the portion taken using the formula:~~

~~$$100C(A_U/A_S),$$~~

~~in which C is the concentration, in mg per mL, of USP Ciclopirox Olamine RS in the *Standard preparation;* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation*, respectively.~~

▲Dissolve 200 mg of Ciclopirox Olamine, accurately weighed, in 2 mL of methanol. Add 38 mL of water, mix, and titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Determine the factor of the 0.1 N sodium hydroxide VS using 100 mg of benzoic acid, accurately weighed, and titrate under the conditions prescribed above. Each mL of 0.1 N sodium hydroxide is equivalent to 26.84 mg of $C_{12}H_{17}NO_2 \cdot C_2H_7NO$.▲*USP27*

BRIEFING

Ciprofloxacin, *USP 26* page 457 and page 2951 of the *First Supplement*. It is proposed to have new acceptance criteria for *Loss on drying* and *Residue on ignition* tests as well as to add a *Microbial limits* test when preparing Ciprofloxacin for Oral Suspension. Other *Labeling* requirements are also added where it is intended for use in preparing injectable dosage forms.

(PA7b: B. Davani; PSD: C. Okeke) RTS—39363-1

Change to read:

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

■Store at 25°, excursion permitted between 15° and 30° and avoid excessive heat.■1S (*USP27*)

Add the following:

■**Labeling—**Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected for further processing during the preparation of injectable dosage forms. Where it is intended for use in preparing Ciprofloxacin for Oral Suspension, it is so labeled. ■1S (*USP27*)

Add the following:

■**Microbial limits** ⟨61⟩—Where it is intended for use in preparing Ciprofloxacin for Oral Suspension, the total microbial count does not exceed 1000 cfu per g and the total combined molds and yeast count does not exceed 100 cfu per g. It also meets the requirement for absence of *Salmonella* and *Escherichia coli*.■1S (*USP27*)

Change to read:

Loss on drying ⟨731⟩—Dry it in vacuum at 120° for 6 hours: it loses not more than 1.0% of its weight,

■except that where it is labeled as intended for use in preparing Ciprofloxacin for Oral Suspension, it loses between 10% and 20% of its weight.■1S (*USP27*)

In-Process Revision

Change to read:

Residue on ignition ⟨281⟩: not more than 0.1%,

■except that where it is intended for use in preparing Ciprofloxacin for Oral Suspension, it is not more than 0.2%.■1S (*USP27*)

Add the following:

■**Other requirements**—Where the label states that it is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩ and *Pyrogen* under *Ciprofloxacin Injection*. Where the label states that Ciprofloxacin must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Pyrogen* under *Ciprofloxacin Injection*.■1S (*USP27*)

BRIEFING

Ciprofloxacin Tablets, *USP 26* page 460. In the *Assay*, it is proposed to use the *Mobile phase* as diluent instead of water to be consistent with that in the drug substance monograph. The appropriate system suitability criteria are also included based on the supporting data received.

(PA7b: B. Davani) RTS—39018-1

In-Process Revision

Change to read:

Assay—

~~*Mobile phase*, *Resolution solution*, and *Chromatographic system*~~—~~Prepare as directed in the *Assay* under *Ciprofloxacin Hydrochloride*.~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Ciprofloxacin Hydrochloride RS quantitatively in water to obtain a solution having a known concentration of about 0.3 mg per mL.~~

~~*Assay preparation*—Transfer 5 Tablets to a 500-mL volumetric flask, add about 400 mL of water, and sonicate for about 20 minutes. Dilute with water to volume, and mix. Dilute an accurately measured volume of this solution quantitatively with water to obtain a solution containing the equivalent of about 0.25 mg of ciprofloxacin per mL.~~

~~*Procedure*—Proceed as directed for *Procedure* in the *Assay* under *Ciprofloxacin Hydrochloride*. Calculate the quantity, in mg, of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in each Tablet taken by the formula:~~

~~$(331.34/367.81)(CL/D)(r_U/r_S)$,~~

~~in which 331.34 and 367.81 are the molecular weights of ciprofloxacin and anhydrous ciprofloxacin hydrochloride, respectively, *C* is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Standard preparation*, calculated on the anhydrous basis, *L* is the labeled quantity, in mg, of ciprofloxacin in each Tablet, *D* is the concentration, in mg per mL, of ciprofloxacin in the *Assay preparation*, based on the labeled quantity per Tablet and the extent of dilution, and r_U and r_S are the ciprofloxacin peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

■*Diluent*—Prepare a filtered and degassed mixture of 0.025 M phosphoric acid, previously adjusted (with triethylamine) to a pH of 2.0 ± 0.1, and acetonitrile (87:13).

Mobile phase—Prepare a filtered and degassed mixture of 0.025 M phosphoric acid, previously adjusted (with triethylamine) to a pH of 3.0 ± 0.1, and acetonitrile (87:13). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Quantitatively dissolve an accurately weighed quantity of USP Ciprofloxacin Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 0.2 mg per mL.

Resolution solution—Dissolve a quantity of USP Ciprofloxacin Ethylenediamine Analog RS in the *Standard preparation* to obtain a solution containing about 0.05 mg per mL.

Assay preparation—Transfer 5 Tablets to a 500-mL volumetric flask, add about 400 mL of *Diluent*, and sonicate for about 20 minutes. Dilute with *Diluent* to volume, and mix. Quantitatively dilute an accurately measured volume of this solution, previously filtered through a 0.45-µm membrane filter, with *Diluent* to obtain a solution containing the equivalent of about 0.20 mg of ciprofloxacin per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 278-nm detector and a 4.6-mm × 25-cm column that contains packing L1 and is operated at 30 ± 1°. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the retention time for ciprofloxacin is between 6.4 and 10.8 minutes; the

relative retention times are about 0.7 for ciprofloxacin ethylenediamine analog and 1.0 for ciprofloxacin; and the resolution, *R*, between the ciprofloxacin ethylenediamine analog peak and the ciprofloxacin peak is not less than 6. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the column efficiency, determined from the ciprofloxacin peak, is not less than 2500 theoretical plates; the tailing factor for the ciprofloxacin peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for the major peaks. Calculate the quantity, in mg, of ciprofloxacin ($C_{17}H_{18}FN_3O_3$) in each Tablet taken by the formula:

$$(331.34/367.81)(CL/D)(r_U/r_S),$$

in which 331.34 and 367.81 are the molecular weights of ciprofloxacin and anhydrous ciprofloxacin hydrochloride, respectively; *C* is the concentration, in mg per mL, of USP Ciprofloxacin Hydrochloride RS in the *Standard preparation*, calculated on the anhydrous basis; *L* is the labeled quantity, in mg, of ciprofloxacin in each Tablet; *D* is the concentration, in mg per mL, of ciprofloxacin in the *Assay preparation*, based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the ciprofloxacin peak areas obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Cod Liver Oil, *USP 26* page 505. It is proposed to update the specifications in this monograph in order to harmonize the requirements with other pharmacopeias. In the Definition, it is proposed to add upper limits for vitamins A and D, since the maximum recommended daily intake for these vitamins is limited in the USA. Suitable antioxidants may be added. When used as dietary supplement, this article usually states the content of omega-3 acids. Therefore, a procedure for the determination of such acids is added, as well as the requirement to indicate their concentrations in the labeling. A new Reference Standard is added to properly identify the fatty acids in the gas chromatograms. The *Identification* test is improved with the addition of a fatty acid profile characteristic of Cod Liver Oil. A limit for anisidine value is added to ensure that the article is not rancid by oxidation of the polyunsaturated acids. A limit for *Mercury* is added given the concern of the authorities about methyl mercury being present in fish-derived products. Finally, it is proposed to substitute the outdated biological procedure for the determination of vitamin D, by a chromatographic procedure harmonized with other international pharmacopeias.

(DSN: G. Giancaspro) RTS—31789-1

Change to read:

» Cod Liver Oil is the partially destearinated fixed oil obtained from fresh livers of *Gadus morrhua* Linné and other species of Fam. Gadidae. Cod Liver Oil contains, in each g, not less than ~~255 µg (850 USP Units)~~

■180 µg (600 USP Units) and not more than 750 µg (2500 USP Units)■1S (*USP27*)
of vitamin A and not less than ~~2.125 µg (85 USP Units)~~

■1.5 µg (60 USP Units) and not more than 6.25 µg (250 USP Units)■1S (*USP27*)
of vitamin D.

Cod Liver Oil may be flavored by the addition of not more than 1 percent of a suitable flavor or a mixture of flavors.

■A suitable antioxidant may be added.■1S (*USP27*)

Change to read:

Labeling—The vitamin A potency and vitamin D potency, when designated on the label, are expressed in USP Units per g of oil. The potencies may be expressed also in metric units, on the basis that 1 USP Vitamin A Unit = 0.3 µg and 40 USP Vitamin D Units = 1 µg.

■Where the content of docosahexaenoic acid or eicosapentaenoic acid are claimed, state their concentrations in mg per g.■1S (*USP27*)

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Change to read:

USP Reference standards ⟨11⟩—*USP Cholecalciferol RS.*

■*USP Cod Liver Oil RS. USP Ergocalciferol RS.*■1S (*USP27*)

Change to read:

Identification — ~~**for vitamin A**— To 1 mL of a 1 in 40 solution in chloroform add 10 mL of antimony trichloride TS: a blue color results immediately.~~

■**A:** *Presence of vitamin A*—To 1 mL of a 1 in 40 solution in chloroform add 10 mL of antimony trichloride TS: a blue color results immediately.

B: *Fatty acid profile*—

Antioxidant solution—Dissolve an accurately weighed quantity of butylated hydroxytoluene in hexanes to obtain a solution having a concentration of 0.05 mg per mL.

Standard solution—Transfer 0.450 g of USP Cod Liver Oil RS, accurately weighed, into a 10-mL volumetric flask, and dissolve in and dilute with *Antioxidant solution* to volume. Transfer 2.0 mL of this solution into a quartz tube, and evaporate with gentle stream of nitrogen. Add 1.5 mL of a 2% solution of sodium hydroxide in methanol, cap tightly with a polytetrafluoroethylene-lined cap, mix, and heat in a water bath for 7 minutes. Cool, add 2 mL of boron trichloride–methanol solution, cover with nitrogen, cap tightly, mix, and heat in a water bath for 30 minutes. Cool to 40° to 50°, add 1 mL of isooctane, cap, and mix in a vortex mixer or shake vigorously for at least 30 seconds. Immediately add 5 mL of saturated sodium chloride solution, cover with nitrogen, cap, and mix in a vortex mixer or shake thoroughly for at least 15 seconds. Allow the upper layer to become clear, and transfer to a separate tube. Shake the methanol layer once more with 1 mL of isooctane, and combine the isooctane extracts. Wash the combine extracts twice with 1 mL of water, and dry over anhydrous sodium sulfate.

System suitability mixture—Prepare a mixture containing accurately weighed and equal amounts of methyl palmitate, methyl stearate, methyl arachidate, and methyl behenate. [NOTE—A suitable mixture is available from Supelco, Bellefonte, PA, as GLC-40 cat. number 1985-1AMP.]

Fatty acid		Lower limit (area %)	Upper limit (area %)
Saturated fatty acids:	Shorthand notation		
Myristic acid	14:0	2.0	6.0
Palmitic acid	16:0	7.0	14.0
Stearic acid	18:0	1.0	4.0
Mono-unsaturated fatty acids:			
Palmetoleic acid	16:1 n-7	4.5	11.5
cis-Vaccenic acid	18:1 n-7	2.0	7.0
Oleic acid	18:1 n-9	12.0	21.0
Gadoleic acid	20:1 n-11	1.0	5.5
Gondoic acid	20:1 n-9	5.0	17.0
Euricic acid	22:1 n-9	0	1.5
Cetoleic acid	22:1 n-11	5.0	12.0
Poly unsaturated fatty acids:			
Linoleic acid	18:2 n-6	0.5	3.0
γ-Linolenic acid	18-3 n-3	0	2.0
Moroctic acid	18:4 n-3	0.5	4.5
Eicosapentanoic acid	20:5 n-3	7.0	16.0
Docosahexanoic acid	22-6n-3	6.0	18.0

Test solution—Proceed as directed for the *Standard solution*, except to use an accurately weighed quantity of Cod Liver Oil.

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Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.25-mm × 30-m fused silica capillary column coated with a 0.25-µm film of G16. The temperature of the detector is maintained at 280° and that of the injection port at 250°. Initially the temperature of the column is equilibrated at 170°, then the temperature is increased at a rate of 1° per minute to 225°, and maintained at 225° for 20 minutes. The carrier gas is helium with a split flow ratio of 1:200. Chromatograph the *Standard solution*, the *System suitability mixture*, and the *Test solution*, and record the peak responses as directed for *Procedure:* the resolution between the peaks in the *Standard solution* due to methyl oleate and methyl *cis*-vaccinate is not less than 1.3, and between methyl gadoleate and methyl gondoate is sufficient for purposes of identification and area measurement; the theoretical area percentages for methyl palmitate, metyl stearate, methyl arachidate, and methyl behenate are 24.4, 24.8, 25.2, and 25.6, respectively. In a suitable instrument, the area percentages from the *System suitability mixture* are within 1% of the theoretical values. The number of fatty acid methyl ester peaks exceeding 0.05% of the total area is at least 24, and the 24 largest peaks of the methyl esters account for more than 90% of the total area. (These correspond to the following, in common elution order: 14:0, 15:0, 16:0, 16:1 n-7, 16:4n-1, 18:0, 18:1 n-9, 18:1 n-7, 18:2 n-6, 18:3 n-3, 18:4 n-3, 20:1 n-11, 20:1 n-9, 20:1 n-7, 20:2 n-6, 20:4 n-6, 20:3 n-3, 20:4 n-3, 20:5 n-3, 22:1 n-11, 22:1 n-9, 21:5 n-3, 22:5 n-3, and 22:6 n-3.)

Procedure—Separately inject by equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the area percent for each fatty acid methyl ester taken by the formula:

$$100(r_a / r_b),$$

in which r_a is the average peak area of each individual fatty acid; and r_b is the total peak area from all peaks in the chromatogram, excepting the solvent front and butylated hydroxytoluene. ■1S (*USP27*)

Add the following:

■**Anisidine value** ⟨401⟩: not more than 30. ■1S (*USP27*)

Add the following:

■**Content of docosohexaenoic acid and eicosapentaenoic acid**—Proceed as directed in the monograph for *Fish Oil Rich in Omega-3 Acids*. ■1S (*USP27*)

Add the following:

■**Mercury**—Proceed as directed in the monograph for *Fish Oil Rich in Omega-3 Acids*. ■1S (*USP27*)

Change to read:

Assay for vitamin D—~~Proceed with Oil as directed for *Biological Method* under *Vitamin D Assay* ⟨581⟩~~

■*Butylated hydroxytoluene solution*—Dissolve a quantity of butylated hydroxytoluene in chromatographic hexane to obtain a solution containing 10 mg per mL.

Aqueous potassium hydroxide solution—Dissolve 800 g of potassium hydroxide in 1000 mL of freshly boiled water, mix, and cool. [NOTE—Prepare this solution fresh daily.]

Alcoholic potassium hydroxide solution—Dissolve 3 g of potassium hydroxide in 50 mL of freshly boiled water, add 10 mL of alcohol, dilute with freshly boiled water to 100 mL, and mix. [NOTE—Prepare this solution fresh daily.]

Ascorbic acid solution—Dissolve 10 g of ascorbic acid in 100 mL of water. [NOTE—Prepare this solution fresh daily.]

Mobile phase A—Prepare a 3 in 1000 mixture of *n*-amyl alcohol in dehydrated hexane.

Mobile phase B—Prepare a mixture of acetonitrile, water, and phosphoric acid (96:3.8:0.2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Internal standard solution—Prepare a solution of USP Ergocalciferol RS in alcohol having a concentration of about 0.5 mg per 100 mL.

Standard preparation—Prepare a solution of USP Cholecalciferol RS in ethyl alcohol, having a known concentration of about 5 µg per mL. Transfer 2.0 mL of this solution and 2.0 mL of the *Internal standard solution* to a round-bottomed flask. Proceed as directed for the *Assay preparation 1* beginning with "Add 5 mL of...".

Assay preparation 1—Transfer an accurately weighed quantity of about 4.00 g of Cod Liver Oil, to a round-bottomed flask. Add 5 mL of *Ascorbic acid solution*, 100 mL of alcohol, and 10 mL of *Aqueous potassium hydroxide solution*, and mix. Reflux the mixture on a steam bath for 30 minutes. Add 100 mL of a sodium chloride solution (1 in 100). Cool rapidly under running water, and transfer the saponified mixture to a 500-mL separator, rinsing the saponification flask with 75 mL of a sodium chloride solution (1 in 100) and then with 150 mL of a mixture of ether and hexane (1:1). Shake the combined saponified mixture and rinsings vigorously for 30 seconds, and allow to stand until both layers are clear. Discard the lower layer. Wash the ether-hexane extracts by shaking vigorously with 50 mL of *Alcoholic potassium hydroxide solution*, and then washing with three 50-mL portions of a sodium chloride solution (1 in 100). Filter the upper layer through 5 g of anhydrous sodium sulfate on a fast filter paper into a 250-mL flask suitable for a rotary evaporator. Wash the filter with 10 mL of a mixture of ether and hexane (1:1), and combine with the extract. Evaporate the solvent at reduced pressure at a temperature not exceeding 30°, and fill with nitrogen when the evaporation is complete. Alternatively evaporate the solvent under a gentle stream of nitrogen at a temperature not exceeding 30°. Dissolve the residue in 1.5 mL of *Mobile phase A*. [NOTE—Gentle heating in an ultrasonic bath may be required. A large fraction of the white residue is cholesterol.]

Assay preparation 2—To 4.00 g of Cod Liver Oil, add 2.0 mL of *Internal standard solution*, and proceed as directed for *Assay preparation 1* beginning with "Add 5 mL of...".

Chromatographic system—Use a chromatograph, operated at room temperature, fitted with an UV detector that monitors absorption at 265 nm; a 25-cm × 4.6-mm stainless steel cleanup column packed with column packing L10 and using *Mobile phase A;* and a 15-cm × 4.6-mm stainless steel analytical column with 5-µm packing L1, and using *Mobile phase B*. Chromatograph five injections of the *Standard preparation*, and measure the peak responses as directed for *Procedure:* the resolution between cholecalciferol and ergocalciferol is not less than 1.4; and the relative standard deviation for the cholecalciferol peak response is not more than 2.0%.

Procedure—Separately inject equal volumes (about 350 µL) of the *Standard preparation*, *Assay preparation 1*, and *Assay preparation 2* into the clean-up chromatographic system. Collect separately the eluates from 2 minutes before until 2 minutes after the retention time of cholecalciferol in a glass tube, containing 1 mL of *Butylated hydroxytoluene solution* and fitted with a hermetic closure. Evaporate each tube under a stream of nitrogen at a temperature not exceeding 30°. Dissolve each residue in 1.5 mL of acetonitrile. Inject equal volumes, not exceeding 200 µL, into the analytical chromatographic system, and measure the peak responses at the retention times corresponding to cholecalciferol and ergocalciferol. Calculate the content of vitamin D, in µg, in the Cod Liver Oil taken by the formula:

$$2C(R_U / R_S),$$

in which C is the concentration, in µg per mL, of the USP Cholecalciferol RS in the *Standard preparation;* R_S is the response of the cholecalciferol relative to the internal standard in the *Standard preparation;* and R_U is the corrected relative response of *Assay preparation 2* calculated by the formula:

$$r_{U2} / [r_{IS2} - (r_{IS1} \times r_{U2} / r_{U1})],$$

in which, r_{U2} and r_{U1} are the peak responses for cholecalciferol in the *Assay preparation 1* and *2*, respectively; and r_{IS1} and r_{IS2} are the peak responses for ergocalciferol in the *Assay preparation 1* and *2*, respectively.■1S (*USP27*)

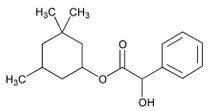
BRIEFING

Cyclandelate, page 353 of *PF 26*(2) [Mar.–April 2000]. This new monograph, which previously appeared in *Pharmacopeial Previews*, is now forwarded to *In-Process Revision*.

(PA5: A. Wilk) RTS—39903-4

Add the following:

■Cyclandelate



$C_{17}H_{24}O_3$ 276.38

3,3,5-Trimethylcyclohexanol α-phenyl-α-hydroxyacetate.

1,5-*cis*-3,3,5-Trimethylcyclohexyl 2-hydroxy-2-phenyl acetate [*456-59-7*].

» Cyclandelate contains not less than 98.0 percent of $C_{17}H_{24}O_3$, calculated on the dried basis.

Packaging and storage—Preserve in ~~well-closed~~ tight, light-resistant containers, and store below 40°, preferably between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Cyclandelate RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 0.5 µg per mL.

Medium: 96 percent alcohol. The solution exhibits absorption maxima between 250 and 254 nm, between 256 and 260 nm, and between 262 and 266 nm.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Dissolve 10 mg of Cyclandelate in 1 mL of alcohol.

Application volume: 5 µL.

Developing solvent system: a mixture of hexane, ethyl acetate, and glacial acetic acid (8:2:1).

Loss on drying ⟨731⟩—Dry 1 g over silica gel for 24 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Chromatographic purity—

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

Test solution—Transfer about 100 mg of Cyclandelate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard solution—Pipet 3.0 mL of the *Test solution* into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 10 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Allow the chromatogram of the *Test solution* to run for a period of time that is about 3 times the

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retention time of cyclandelate. The total area of all the peaks from the *Test solution*, other than the peak obtained from cyclandelate, is not greater than the peak area of cyclandelate obtained from the *Standard solution:* not more than 3.0% of total impurities is found.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (4:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve accurately weighed quantities of USP Cyclandelate RS and dicyclohexyl phthalate in *Mobile phase* to obtain a solution having known concentrations of about 0.2 mg per mL and 0.08 mg per mL, respectively.

Standard preparation—Dissolve an accurately weighed quantity of USP Cyclandelate RS in *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer about 100 mg of Cyclandelate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 228-nm detector and a 4.0-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between cyclandelate and dicyclohexyl phthalate is not less than 7. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{17}H_{24}O_3$ in the portion of Cyclandelate taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Cyclandelate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

BRIEFING

Cyclobenzaprine Hydrochloride, *USP 26* page 527. It is proposed to correct the concentration of the solvents used in the *Standard solution* in the test for *Organic volatile impurities*. This change is necessary because the test requires different concentrations of solvents than those described in the general test chapter *Organic Volatile Impurities* ⟨467⟩. The proposal reflects the actual concentrations that have to be used to be congruent with the actual chapter, but respecting the limit of 50 µg per g of chloroform.

(PA3: S. Salado) RTS—39640-3

Change to read:

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Test solution: 200 mg per mL.

Standard solution—Proceed as directed except to use 100.0 µg of methylene chloride, ~~10.0 µg~~

■12.0 µg■1S (*USP27*) of chloroform, ~~and 20.0 µg each of benzene,~~

■76.0 µg of■1S (*USP27*) 1,4-dioxane, and

■16.0 µg of■1S (*USP27*) trichloroethylene.

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BRIEFING

Dichlorphenamide, *USP 26* page 594. A revision to the monograph is proposed to reflect the proper use of the USP Dichlorphenamide Reference Standard in the *Assay.* The revision is in accordance with changes to the directions of use for the Reference Standard.

(PA6: L. Evans) RTS—39834-1

Change to read:

Assay—

Mobile solvent—Prepare a suitable solution of 0.02 M monobasic sodium phosphate and 0.02 M dibasic sodium phosphate in acetonitrile and water (approximately 1:1) such that the retention time of Dichlorphenamide is approximately 6 minutes.

Standard preparation—Dissolve ~~a previously dried and~~ ■an■1S (*USP27*) accurately weighed quantity of USP Dichlorphenamide RS in *Mobile solvent* to obtain a solution containing about 1 mg per mL.

Assay preparation—Accurately weigh about 50 mg of Dichlorphenamide, and prepare as directed for *Standard preparation*.

Procedure—Introduce separately 20-µL portions of the *Assay preparation* and the *Standard preparation* into a high-pressure liquid chromatograph (see *Chromatography* ⟨621⟩) operated at 25°, by means of a suitable microsyringe or sampling valve, adjusting the operating parameters such that the peak obtained with the *Standard preparation* is full-scale. Typically, the apparatus is fitted with a 4-mm × 30-cm column, packed with packing L1, is equipped with an UV detector capable of monitoring absorption at 280 nm and a suitable recorder, and is capable of operating at a column pressure of up to 3500 psi. Five replicate injections of the *Standard preparation* show a relative standard deviation of not more than 1.5%. Calculate the quantity, in mg, of $C_6H_6Cl_2N_2O_4S_2$ in the portion of Dichlorphenamide taken by the formula:

$$50C(A_U/A_S),$$

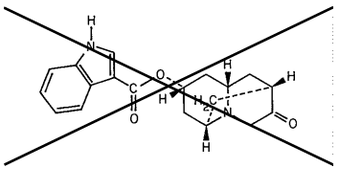
in which C is the concentration, in mg per mL, of USP Dichlorphenamide RS in the *Standard preparation;* and A_U and A_S are the area responses obtained at equivalent retention times from the *Assay preparation* and the *Standard preparation,* respectively.

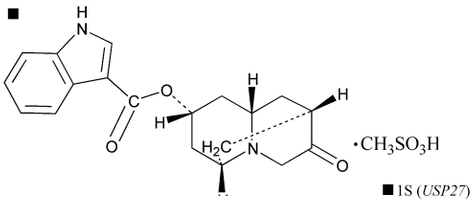
BRIEFING

Dolasetron Mesylate, *USP 26* page 658. Comments were received that the use of some brands of L7 columns (such as Zorbax RX-C8) for the *Related compounds* test results in an inverted order of elution for the indole and dolasetron mesylate peaks. It is proposed to add a procedure for conditioning the columns that would result in the correct elution order. It was also shown that certain columns such as SynChropac RP8 and Zorbax SB-C8 exhibited the correct elution order and did not require conditioning. It is also proposed to correct the formulas under the *Related compounds* test. The graphic structure is also corrected.

(PA4: E. Gonikberg) RTS—39953-1

Change to read:



■ 

■1S (*USP27*)

$C_{19}H_{20}N_2O_3 \cdot CH_4O_3S \cdot H_2O$ 438.50

1*H*-Indole-3-carboxylic acid, octahydro-3-oxo-2,6-methano-2*H*-quinolizin-8-yl ester, (2α,6α,8α, 9aβ)-, monomethanesulfonate monohydrate.

Indole-3-carboxylic acid, ester with (8*r*)-hexahydro-8-hydroxy-2,6-methano-2*H*-quinolizin-3(4*H*)-one, monomethanesulfonate monohydrate [*115956-13-3*].

Change to read:

Related compounds—

0.01 M Dibasic ammonium phosphate solution—Dissolve 132.1 g of dibasic ammonium phosphate in 1000 mL of water. Dilute 10.0 mL of this solution with about 990 mL of water, adjust with 2.0 M phosphoric acid to a pH of 7.0, and mix.

Diluent—Prepare a mixture of water and acetonitrile (4:1).

Solution A—Prepare a filtered and degassed mixture of *0.01 M Dibasic ammonium phosphate solution* and acetonitrile (1000 : 53).

Solution B—Prepare a filtered and degassed mixture of acetronitrile and *0.01 M Dibasic ammonium phosphate solution* (795 : 295).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution of indole and USP Dolasetron Mesylate RS in *Diluent* having known concentrations of about 0.004 mg per mL and 0.03 mg per mL, respectively.

Standard solution 1—Dissolve an accurately weighed quantity of USP Dolasetron Mesylate RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.03 mg per mL.

Standard solution 2—Dissolve accurately weighed quantities of USP Dolasetron Mesylate RS and USP Dolasetron Mesylate Related Compound A RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 6 mg per mL and 0.0072 mg per mL, respectively.

In-Process Revision

Test solution—Transfer about 150 mg of Dolasetron Mesylate, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–28	100→0	0→100	linear gradient
28–38	250	100	isocratic
38–40	0→100	100→0	linear gradient
40–50	100	0	isocratic

Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between the first eluting peak, indole, and the second eluting peak, dolasetron mesylate, is not less than 1.5.

■[NOTE—If the dolasetron mesylate peak is found to elute before the indole peak, condition the column as follows. Fill up the column with *Solution A*, plug the column, and place the column in a convection oven at 105° for about 16 hours. Retest the column.]■1S (*USP27*)

Chromatograph *Standard solution 1*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of *Standard solution 1*, *Standard solution 2*, and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of dolasetron mesylate related compound A in the portion of Dolasetron Mesylate taken by the formula:

~~$(181.2/217.8)1000(r_U/r_S)$,~~

■$2500(181.2/217.8)(C_{RC}/W)(r_U/r_S)$,■1S (*USP27*)

in which 181.2 and 217.8 are the molecular weights of dolasetron mesylate related compound A base and dolasetron mesylate related compound A hydrochloride, respectively;

■C_{RC} is the concentration, in mg per mL, of USP Dolasetron Mesylate Related Compound A RS in *Standard solution 2;* W is the weight, in mg, of Dolasetron Mesylate taken to prepare the *Test solution*;■1S (*USP27*)

and r_U and r_S are the peak areas for dolasetron mesylate related compound A obtained from the *Test solution* and *Standard solution 2*, respectively: not more than 0.1% of dolasetron mesylate related compound A is found. Calculate the percentage of each impurity (other than dolasetron mesylate related compound A) in the portion of Dolasetron Mesylate taken by the formula:

~~$200(r_i/r_S)$,~~

■$2500(C/W)(r_i/r_S)$,■1S (*USP27*)

in which

■C is the concentration, in mg per mL, of USP Dolasetron Mesylate RS in *Standard solution 1;* W is as defined above;■1S (*USP27*)

r_i is the peak area for each impurity obtained from the *Test solution;* and r_S is the peak area for dolasetron mesylate obtained from *Standard solution 1:* not more than 0.1% of any individual impurity is found; and not more than 0.3% of total impurities is found.

BRIEFING

Ferrous Fumarate and Docusate Sodium Extended-Release Tablets, *USP 26* page 784. It is proposed to add a *Drug release* test to this monograph.

(BPC: M. Marques) RTS—35820-1

Add the following:

■**Drug release** ⟨724⟩—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Times: 1 and 3 hours.

Determine the amount of Fe (II) dissolved, in filtered portions of the solution under test, employing the method described under *Assay for ferrous fumarate* with the following modification.

Standard solution—Transfer the appropriate amount of *Iron stock solution* to a volumetric flask, and dilute with 0.1 N hydrochloric acid in such a way that the final concentration is similar to that expected in the solution under test.

In-Process Revision

Tolerances—The percentages of the labeled amount of Fe (II) dissolved at the times specified conform to *Acceptance Table 1* under *Drug Release* ⟨724⟩.

Time (hours)	Amount dissolved
1	between 40% and 75%
3	not less than 80%■1S (*USP27*)

BRIEFING

Fexofenadine Hydrochloride Capsules, page 1793 of *PF* 28(6) [Nov.–Dec. 2002]. It is proposed to add an early time point to the *Dissolution* test to better control the quality of the product, in consideration that the drug substance can exist in two pseudopolymorphic forms, anhydrous and hydrate.

(BPC: M. Marques) RTS—39653-3

Add the following:

■Fexofenadine Hydrochloride Capsules

» Fexofenadine Hydrochloride Capsules contain not less than 93.0 percent and not more than 107.0 percent of the labeled amount of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$).

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

USP Reference standards ⟨11⟩—*USP Fexofenadine Hydrochloride RS. USP Fexofenadine Related Compound A RS. USP Fexofenadine Related Compound B RS.*

Identification—

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

B: *Infrared Absorption* ⟨197K⟩—

Test specimen—Empty the contents of several Capsules, equivalent to about 60 mg of fexofenadine hydrochloride, into a suitable capped tube. Add 10 mL of a mixture of acetonitrile and methanol (10:1), and shake until the sample is dispersed. Allow to settle. Decant, filter, and collect the supernatant in a suitable beaker. Evaporate the solvent to near dryness by using a stream of nitrogen and with gentle heating from an appropriate source (steam, low-temperature hot plate). While still warm, add 5 mL of water and 5 drops of diluted hydrochloric acid, and stir to induce precipitation. Chill in an ice bath for about 30 minutes. Pass through a 10- to 15-µm filtering crucible with fritted disk. Dry the precipitate in an air oven for 1 hour at 105°.

Water, *Method I* ⟨921⟩: between 3.5% and 8.0%, the titration being performed at 50° and the titration vessel being kept in a heated water jacket.

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Times: 15 and 45 minutes.

Determine the amount of $C_{32}H_{39}NO_4 \cdot HCl$ dissolved by employing the following method.

Buffer solution—Dissolve 1.0 g of monobasic sodium phosphate, 0.5 g of sodium perchlorate, and ~~0.5 mL~~ 0.3 mL of phosphoric acid in 300 mL of water, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (700 : 300), and mix. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

In-Process Revision

System suitability stock solution—[NOTE—A small amount of glacial acetic acid, not to exceed 5% of the total volume, is used, if necessary, to dissolve USP Fexofenadine Hydrochloride Related Compound A RS.] Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride Related Compound A RS in water to obtain a solution having a known concentration of 0.44 mg per mL.

System suitability solution—Prepare a solution of USP Fexofenadine Hydrochloride RS in *System suitability stock solution* containing about 0.01 mg of USP Fexofenadine Hydrochloride Related Compound A RS and 0.06 mg of USP Fexofenadine Hydrochloride RS per mL.

Standard solution—[NOTE—A small amount of methanol, not to exceed 0.5% of the total volume, is used, if necessary, to dissolve USP Fexofenadine Hydrochloride RS.] Dissolve an accurately weighed quantity of USP Fexofenadine Hydrochloride RS in water to obtain a solution having a known concentration of 0.07 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 10-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between fexofenadine and fexofenadine hydrochloride related compound A is not less than 2.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and filtered portions of the solution under test into the chromatograph, record the chromatograms, and measure the responses for the fexofenadine peaks. Calculate the quantity of $C_{32}H_{39}NO_4 \cdot HCl$ dissolved.

Tolerances—Not less than 50% (*Q*) of the labeled amount of $C_{32}H_{39}NO_4 \cdot HCl$ is dissolved in 15 minutes. Not less than 75% (*Q*) of the labeled amount of $C_{32}H_{39}NO_4 \cdot HCl$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Related compounds—

Phosphate–perchlorate buffer—Prepare as directed in the *Assay.*

Diluting solution, *Mobile phase*, *System suitability preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Fexofenadine Hydrochloride*.

Standard solution—Use the *Standard preparation*, prepared as directed in the *Assay* under *Fexofenadine Hydrochloride*.

Test solution—Use the *Assay stock preparation*, prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of fexofenadine hydrochloride related compound A in the portion of Capsules taken by the formula:

$$100C(r_U / r_S),$$

in which *C* is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride Related Compound A RS in the *Standard solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution*, respectively: ~~not more than 0.3% of fexofenadine hydrochloride related compound A is found.~~ not more than 0.3% of fexofenadine related compound A, not more than 0.2% of decarboxylated degradant, and not more than 0.1% of any other unknown impurity is found; and not more than 0.5% of total impurities is found.

In-Process Revision

Assay—

Phosphate–perchlorate buffer—Dissolve 6.64 g of monobasic sodium phosphate and 0.84 g of sodium perchlorate in 1000 mL of water. Adjust with phosphoric acid to a pH of ~~4.0~~ 2.0.

Diluting solution, *Mobile phase*, *System suitability preparation*, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Fexofenadine Hydrochloride*.

Assay stock preparation—Remove, as completely as possible, the contents of not fewer than 20 Capsules, mix the combined contents, and finely powder by using a mortar and pestle. Transfer a portion of the powder, equivalent to about 50 mg of fexofenadine hydrochloride, accurately weighed, to a 50-mL volumetric flask. Add 40 mL of *Diluting solution*, and shake by mechanical means for 60 minutes. Sonicate for about 2 minutes. Allow to cool to room temperature, dilute with *Diluting solution* to volume, and mix.

Assay preparation—Transfer 3.0 mL of the *Assay stock preparation* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of fexofenadine hydrochloride ($C_{32}H_{39}NO_4 \cdot HCl$) in the portion of Capsules taken by the formula:

$$833.3C(r_U / r_S)$$

in which C is the concentration, in mg per mL, of USP Fexofenadine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

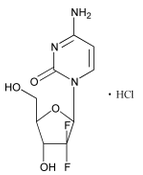
BRIEFING

Gemcitabine Hydrochloride, page 3141 of *PF* 27(5) [Sept.–Oct. 2001]; **Gemcitabine for Injection,** page 3142 of *PF* 27(5) [Sept.–Oct. 2001]. These new monographs, which previously appeared in *Pharmacopeial Previews*, are now forwarded to *In-Process Revision*. On the basis of comments received, minor changes are proposed in the *Assay* of *Gemcitabine Hydrochloride*. It is also proposed to add storage conditions to the *Packaging and storage* section and to add a *Chromatographic purity* test.

(PA6: L. Evans) RTS—38539-2

Add the following:

■Gemcitabine Hydrochloride



$C_9H_{11}F_2N_3O_4 \cdot HCl$ 299.66

Cytidine, 2′-deoxy-2′,2′-difluro-, monohydrochloride.

2′-Deoxy-2′,2′-difluorocytidine monohydrochloride (b-isomer) [*122111-03-9*].

» Gemcitabine Hydrochloride contains not less than 97.5 percent and not more than 101.5 percent of $C_9H_{11}F_2N_3O_4 \cdot HCl$, calculated on the as-is basis.

In-Process Revision

Caution—Gemcitabine Hydrochloride is a potent cytotoxic agent. Great care should be taken to prevent inhaling particles and exposing the skin to it.

Packaging and storage—Preserve in ~~well-closed~~ tight containers, and store at controlled room temperature.

Labeling—Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Gemcitabine Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of the tests for *Chloride* ⟨191⟩.

Specific rotation ⟨781S⟩: between +43° and +50°, at 20°.

Test solution: 10 mg per mL.

pH ⟨791⟩: between 2.0 and 3.0, in a solution containing 10 mg per mL.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method I* ⟨231⟩: 0.001%.

Chromatographic purity—

Solution A—Proceed as directed for *Mobile phase* in the *Assay.*

Solution B—Prepare filtered and degassed methanol.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed under *Chromatographic system*. Make adjustments, if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Gemcitabine Hydrochloride RS and USP Cytosine RS in water, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 2 µg per mL of each.

Test solution—Transfer about 50 mg of Gemcitabine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed under *Assay.* The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–8	97	3	Isocratic
8–13	97→50	3→50	Linear gradient
13–20	50	50	Isocratic
20–25	50→97	50→3	Re-equilibrate

Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5 for gemcitabine α-anomer and 1.0 for gemcitabine; the resolution, *R*, between gemcitabine α-anomer and gemcitabine is not less than 8.0; and the tailing factor for gemcitabine is not more than 1.5. Chromatograph the standard solution and record the peak responses as directed for *Procedure:* the relative retention times are about 0.1 for cytosine and 1.0 for gemcitabine; the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject a volume (about 20µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of cytosine in the portion of Gemcitabine taken by the formula:

$$2.5(C_c / W)(r_t / r_s)$$

In-Process Revision

in which C_c is the concentration of USP Cytosine RS in the *Standard solution*, in µg per mL, W is the weight, in mg, of Gemcitabine taken, r_t is the peak response for cytosine in the *Test solution*, and r_s is the response for cytosine in the *Standard solution:* not more than 0.1% of cytosine is found. Calculate the percentage of each impurity other than cytosine in the portion of Gemcitabine taken by the formula:

$$2.5(C_s / W)(r_i / r_s)$$

in which C_s is the concentration of USP Gemcitabine Hydrochloride RS in the *Standard solution*, in µg per mL, W is the weight, in mg, of Gemcitabine taken, r_i is the peak response for each impurity in the *Test solution*, and r_s is the response due to gemcitabine in the *Standard solution:* not more than 0.1% of gemcitabine α-anomer or any other individual impurity is found and the sum of all impurities is not more than 0.2%. Exclude from the sum of all impurities any peaks that are below the limit of quantitation (0.02%).

Other requirements—Where the label states that Gemcitabine Hydrochloride is sterile, it meets the requirements for *Bacterial endotoxins* and *Sterility* under *Gemcitabine Hydrochloride for Injection.* Where the label states that Gemcitabine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Gemcitabine Hydrochloride for Injection.*

Assay—

Mobile phase—Prepare a filtered and degassed solution containing 13.8 g of monobasic sodium phosphate and 2.5 mL of phosphoric acid in 1000 mL of water. [NOTE—The pH of this solution is between 2.4 and 2.6.]

System suitability solution—Transfer about 10 mg of Gemcitabine Hydrochloride to a small vial, add 4 mL of a solution containing 168 mg of potassium hydroxide per mL of methanol, cap tightly, and sonicate. Heat at 55° for 6 to 16 hours, allow to cool, and transfer the contents to a 100-mL volumetric flask with successive washes of 1% (v/v) phosphoric acid. Dilute with 1% phosphoric acid to volume, and mix. [NOTE—This solution contains about 0.02 mg per mL of gemcitabine α-anomer.]

Standard preparation—Dissolve an accurately weighed quantity of USP Gemcitabine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Transfer about 20 mg of Gemcitabine Hydrochloride, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.2 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, R, between the gemcitabine α-anomer and gemcitabine is not less than 8.0; and the tailing factor determined from gemcitabine is not more than 1.5. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_9H_{11}F_2N_3O_4 \cdot HCl$ in the portion of Gemcitabine Hydrochloride taken by the formula:

$$200C(r_U / r_S),$$

In-Process Revision

in which C is the concentration, in mg per mL, of USP Gemcitabine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

BRIEFING

Gemcitabine for Injection, page 3142 of *PF* 27(5) [Sept.–Oct. 2001]—See briefing under *Gemcitabine Hydrochloride*.

(PA6: L. Evans) RTS—38539-1

Add the following:

■Gemcitabine for Injection

» Gemcitabine for Injection contains an amount of Gemcitabine Hydrochloride equivalent to not less than 95 percent and not more than 105 percent of the labeled amount of gemcitabine ($C_9H_{11}F_2N_3O_4$).

Caution—Gemcitabine Hydrochloride is a potent cytotoxic agent. Great care should be taken to prevent inhaling particles and exposing the skin to it.

Packaging and storage—Preserve in *Containers for Sterile Solids*, as described under *Injections* ⟨1⟩. Store at controlled room temperature. Do not refrigerate after reconstitution.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Gemcitabine Hydrochloride RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩.

Solution: 16 µg per mL.

Medium: 0.14 M phosphate buffer with a pH of 2.5, prepared as follows. Add 13.8 g of monobasic sodium phosphate and 2.5 mL of phosphoric acid to 1000 mL of purified water.

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

Clarity of solution—Dissolve it in the solvent and at the concentration recommended in the labeling: not more than 10t (see *Spectrophotometry and Light-Scattering* ⟨851⟩), determined by ratio turbidimetry within 15 minutes of reconstitution, corrected for a diluent blank.

Bacterial endotoxins ⟨85⟩—It contains not more than 0.05 USP Endotoxin Unit per mg of gemcitabine.

Sterility ⟨71⟩: meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined.*

Uniformity of dosage units ⟨905⟩: meets the requirements for *Weight Variation.*

pH ⟨791⟩: between 2.7 and 3.3, in a solution containing 40 mg in each mL of 0.9% sodium chloride solution.

Particulate matter ⟨788⟩: meets the requirements for small-volume injections.

Chromatographic purity—

Mobile phase, *Standard solution*, *System Suitability Solution* and *Chromatographic system*—Proceed as directed under the test for *Chromatographic purity* for *Gemcitabine Hydrochloride.*

Test solution—Reconstitute the vial with an appropriate amount of water to achieve a solution of 2 mg per mL, based on the labeled content of gemcitabine.

In-Process Revision

Procedure— Proceed as directed under the *Chromatographic purity* for *Gemcitabine Hydrochloride*. Calculate the amount of cytosine expressed as percentage of Gemcitabine Hydrochloride by the formula:

$$0.1(263.20/299.66)(C_cV/L)(r_t / r_s)$$

in which 299.66 is the molecular weight of Gemcitabine Hydrochloride, 263.20 is the molecular weight of gemcitabine, V is the volume, in mL, of water used to reconstitute the vial, L is the labeled amount of gemcitabine in the vial, in mg, C_c is the concentration of USP Cytosine RS in the *Standard solution*, in µg per mL, r_t is the peak response for cytosine in the *Test solution*, and r_s is the response for cytosine in the *Standard solution:* not more than 0.1% of cytosine is found. Similarly, calculate the amount of each impurity other than cytosine, expressed as a percentage of gemcitabine hydrochloride, by the formula:

$$0.1(263.20/299.66)(C_sV/L)(r_i / r_s)$$

in which 299.66 is the molecular weight of Gemcitabine Hydrochloride, 263.20 is the molecular weight of gemcitabine, V is the volume, in mL, of water used to reconstitute the vial, L is the labeled amount of gemcitabine in the vial, in mg, C_s is the concentration of USP Gemcitabine Hydrochloride RS in the *Standard solution*, in µg per mL, r_i is the response for gemcitabine α-anomer or any other individual impurity, and r_s is the peak response for gemcitabine in the *Test solution*. Not more than 0.1% of gemcitabine α-anomer is found, not more than 0.2% each of any other impurity is found, and the sum of all impurities is not more than 0.3%. Exclude from the sum of all impurities any peaks that are below the limit of quantitation (0.02%).

Assay—

Mobile phase, *System suitability solution*, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Gemcitabine Hydrochloride.*

Assay preparation—Constitute a suitable number of vials of Gemcitabine for Injection with purified water to obtain a solution having a concentration of about 0.1 mg per mL, based on the labeled content of gemcitabine.

Procedure—Proceed as directed in the *Assay* under *Gemcitabine Hydrochloride.* Calculate the amount, in mg, of gemcitabine ($C_9H_{11}F_2N_3O_4$) in each vial of Gemcitabine for Injection taken by the formula:

$$(263.20/299.66)(CV/N)(r_U / r_S),$$

in which 263.20 and 299.66 are the molecular weights of gemcitabine and gemcitabine hydrochloride, respectively; V is the total volume, in mL, of the *Assay preparation; N* is the number of vials taken; and the other terms are as defined therein.■1S (*USP27*)

BRIEFING

Idoxuridine, *USP 26* page 951. The calculation of respective absorptivities in the UV test has been clarified to reflect the new labeling requirement for the USP Idoxuridine RS.

(PA7b: B. Davani) RTS—39913-1

Change to read:

Identification—
A: *Infrared Absorption* ⟨197M⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 35 µg per mL.
Medium: pH 12.0 buffer (prepared from 7.46 g of potassium chloride and 24 mL of 1 N sodium hydroxide dissolved in 2000 mL of water). Absorptivities at 279 nm, calculated on the dried basis

■for the test sample only,■1S (*USP27*)
do not differ by more than 2.0%.

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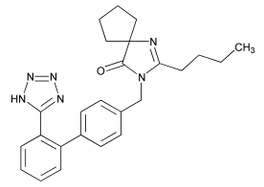
BRIEFING

Irbesartan, page 7156 of *PF* 24(6) [Nov.–Dec. 1998]; **Irbesartan Tablets,** page 7157 of *PF* 24(6) [Nov.–Dec. 1998]; **Irbesartan and Hydrochlorothiazide Tablets,** page 7158 of *PF* 24(6) [Nov.–Dec. 1998]. These new monographs, which previously appeared in *Pharmacopeial Previews*, are now forwarded with minor editorial style changes to *In-Process Revision*. The molecular weight of Irbesartan is revised to reflect the current atomic weight values published in *USP 26*.

(PA5: A. Wilk) RTS—39894-4

Add the following:

■Irbesartan



$C_{25}H_{28}N_6O$ ~~428.54~~ 428.53

1,3-Diazaspiro[4.4]non-1-en-4-one, 2-butyl-3-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl]-.

2-Butyl-3-[*p*-(*o*-1*H*-tetrazol-5-ylphenyl)benzyl]-1,3-diazaspiro[4.4]non-1-en-4-one [*138402-11-6*].

» Irbesartan contains not less than 98.0 percent and not more than 102.0 percent of $C_{25}H_{28}N_6O$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers.

USP Reference standards ⟨11⟩—*USP Irbesartan RS.*

Identification, *Infrared Absorption* ⟨197K⟩.

Water, *Method I* ⟨921⟩: not more than 0.5%.

Chromatographic purity—

Diluent, *Triethylamine solution*, *Mobile phase*, and *Chromatographic system*—Proceed as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Irbesartan taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all the peaks: not more than 0.5% of any individual impurity is found, and not more than 1.0% of total impurities is found.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Assay—

Diluent—Prepare a solution of phosphoric acid (1 in 100).

Triethylamine solution—Add 1.0 mL of triethylamine to 1000 mL of water, mix, and adjust with phosphoric acid to a pH of 3.5.

Mobile phase—Prepare a filtered and degassed mixture of *Triethylamine solution* and acetonitrile (1:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Irbesartan RS in *Diluent* to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Irbesartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a fluorometric detector that has an excitation wavelength of 250 nm and an emission wavelength of 371 nm, and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard*

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preparation, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the irbesartan peaks. Calculate the quantity, in mg, of $C_{25}H_{28}N_6O$ in the portion of Irbesartan taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Irbesartan RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

BRIEFING

Irbesartan Tablets, page 7157 of *PF* 24(6) [Nov.–Dec. 1998]—See briefing under *Irbesartan*.

(PA5: A. Wilk) RTS—39894-5

Add the following:

■Irbesartan Tablets

» Irbesartan Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of irbesartan ($C_{25}H_{28}N_6O$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Irbesartan RS.*

Identification—The relative retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: 0.01 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_{25}H_{28}N_6O$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 254 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Irbesartan RS diluted in the same *Medium*.

Tolerances—Not less than 75% (Q) of the labeled amount of $C_{25}H_{28}N_6O$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Chromatographic purity—

Diluent, *Triethylamine solution*, *Mobile phase*, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Irbesartan*.

Test solution—Use the *Assay preparation.*

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 1.0% of any individual impurity is found, and not more than 2.0% of total impurities is found.

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Assay—

Diluent, *Triethylamine solution*, and *Mobile phase*—Proceed as directed in the *Assay* under *Irbesartan*.

Standard preparation—Dissolve an accurately weighed quantity of USP Irbesartan RS in *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 30 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 10 mg of irbesartan, to a 100-mL volumetric flask. Add about 80 mL of *Diluent,* and stir on a magnetic stir plate for 15 minutes. Dilute with *Diluent* to volume, and mix. Centrifuge a portion of this solution for 10 minutes, and use the clear supernatant.

Chromatographic system—Prepare as directed in the *Assay* under *Irbesartan*. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and record the responses for the major peaks. Calculate the quantity, in mg, of irbesartan ($C_{25}H_{28}N_6O$) in the portion of Tablets taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Irbesartan RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S *(USP27)*

BRIEFING

Irbesartan and Hydrochlorothiazide Tablets, page 7158 of *PF* 24(6) [Nov.–Dec. 1998]—See briefing under *Irbesartan*.

(PA5: A. Wilk) RTS—39894-6

Add the following:

■Irbesartan and Hydrochlorothiazide Tablets

» Irbesartan and Hydrochlorothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of irbesartan ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Irbesartan RS. USP Hydrochlorothiazide RS.*

Identification—The relative retention time of the major peaks in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: 0.01 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amounts of irbesartan ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved by employing the following method.

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

Procedure—~~[NOTE—Use peak areas where peak responses are indicated.]~~ Separately inject equal volumes (about 50 µL) of the Standard solution and filtered portions

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of the solutions under test into the chromatograph, record the chromatograms, and measure the ~~responses~~ areas for the major peaks. Calculate the quantities of irbesartan ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved in comparison with a Standard solution having known concentrations of USP Irbesartan RS and USP Hydrochlorothiazide RS in the same *Medium* and similarly chromatographed.

Tolerances—Not less than 75% (*Q*) of the labeled amounts of $C_{25}H_{28}N_6O$ and $C_7H_8ClN_3O_4S_2$ are dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Triethylamine solution—Add 1.0 mL of triethylamine to 1000 mL of water, mix, and adjust with phosphoric acid to a pH of 3.5.

Mobile phase—Prepare a filtered and degassed mixture of *Triethylamine solution* and acetonitrile (1:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 25 mg of USP Hydrochlorothiazide RS, accurately weighed, to a 100-mL volumetric flask. Add 25*J* mg of USP Irbesartan RS, accurately weighed, *J* being the ratio of the labeled amount, in mg, of irbesartan to the labeled amount, in mg, of hydrochlorothiazide per Tablet. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of powder, equivalent to about 25 mg of hydrochlorothiazide, to a 100-mL volumetric flask. Add about 80 mL of *Mobile phase,* and stir on a magnetic stir plate for 15 minutes. Dilute with *Mobile phase* to volume, and mix. Centrifuge a portion of this solution for 10 minutes, and use the clear supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak ~~responses~~ areas as directed for *Procedure:* the resolution, *R,* between hydrochlorothiazide and irbesartan is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, and record the ~~responses~~ areas for the major peaks. Calculate the quantities, in mg, of irbesartan ($C_{25}H_{28}N_6O$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken by the formula:

$$100C(r_U / r_S),$$

in which *C* is the concentration, in mg per mL, of the appropriate Reference Standard in the *Standard preparation;* and r_U and r_S are the peak responses of the corresponding analyte obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■1S (*USP27*)

BRIEFING

Isradipine Capsules, page 4334 of *PF* 23(4) [July–Aug. 1997]. This new monograph, which previously appeared in *Pharmacopeial Previews*, is now being forwarded to *In-Process Revision*.

(PA5: A. Wilk) RTS—39894-3

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Add the following:

■Isradipine Capsules

» Isradipine Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{19}H_{21}N_3O_5$.

Packaging and storage—Store in a tight container at controlled room temperature. Protect from light.

USP Reference standards ⟨11⟩—*USP Isradipine RS. USP Isradipine Related Compound A RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Solution—Transfer the contents of one Capsule into a suitable volumetric flask, dissolve the contents in the *Medium* by mechanical shaking for 15 minutes, and dilute with the *Medium* to obtain a solution containing 25 µg of isradipine per mL.

Medium: methanol.

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

Uniformity of dosage units ⟨905⟩: meet the requirements.

NOTE—Isradipine is light sensitive. Throughout the following procedures, protect test or assay specimens, the Reference Standards, and solutions containing them from unnecessary exposure to light. Use low-actinic glassware, unless otherwise directed.

Chromatographic purity—

Mobile phase, *Resolution solution*, and *Chromatographic system*—Proceed as directed in the test for *Chromatographic purity* under *Isradipine.*

Standard solution—Dissolve an accurately weighed quantity of USP Isradipine RS in *Mobile phase*, with the aid of sonication if necessary, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1 µg per mL. [NOTE—If necessary, use 1 mL of methanol per 20 mL of *Mobile phase* to dissolve the Reference Standard prior to diluting with *Mobile phase.*]

Test solution—Use the *Assay preparation.*

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks: the sum of all peak responses, other than that of isradipine, from the *Test solution* is not more than three times the isradipine response obtained from the *Standard solution* (1.5%); and no single peak response is greater than that of the isradipine peak response obtained from the *Standard solution* (0.5%).

Assay—

Mobile phase, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Isradipine.*

Assay preparation—Remove, as completely as possible, the contents of not fewer than 20 Capsules, and mix the combined contents. Transfer an accurately weighed quantity, equivalent to about 25 mg of isradipine, to a 100-mL volumetric flask. Add 5.0 mL of methanol and 5.0 mL of *Mobile phase*, and sonicate at room temperature for 15 minutes. Shake for 15 minutes in a mechanical shaker. Dilute with *Mobile phase* to volume, mix, and filter, discarding the first 5 mL of the filtrate.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

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measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{19}H_{21}N_3O_5$ in the portion of Capsules taken by the formula:

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Isradipine RS in the *Standard preparation;* and r_U and r_S are the isradipine peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

BRIEFING

Ketamine Hydrochloride, *USP 26* page 1045 and page 1411 of *PF* 28(5) [Sept.–Oct. 2002]. On the basis of comments received, several changes are being proposed. In the test for *Related compounds* as proposed in *PF* 28(5), there are changes to the preparation of the *Standard solution* and the *Test solution*, the *Chromatographic system*, and the *Procedure*. These changes are being made in the interest of clarification and simplification of the method. In the *Assay*, the proposed changes published on page 1140 of *PF* 28(4) are canceled, and in the *Chromatographic system* in the *Assay* there is a new proposal to lower the resolution from 9.4 to 2.0. Interested parties are encouraged to submit comments to the USP Expert Committee on Veterinary Drugs (Standards).

(VET: I. DeVeau) RTS—38679-1; 39357-1; 39357-2; 39412-1; 39428-1; 39504-1

Change to read:

Related compounds—

~~*Buffer*, *Mobile phase*, and *System suitability solution*—Proceed as directed in the *Assay*.~~

~~*Standard solution*—Transfer 4.0 mL of the *System suitability solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a solution having known concentrations of about 0.002 mg each of USP Ketamine Hydrochloride RS and USP Ketamine Related Compound A RS per mL.~~

~~*Test solution*—Transfer about 100 mg of Ketamine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, add about 30 mL of *Mobile phase*, and sonicate to dissolve. Dilute with *Mobile phase* to volume, and mix.~~

~~*Chromatographic system*—Proceed as directed in the *Assay*. To evaluate the system suitability requirements, use the *System suitability solution* and the *Standard preparation*, as prepared in the *Assay*.~~

~~*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of ketamine related compound A in the portion of Ketamine Hydrochloride taken by the formula:~~

~~$5000(C/W)(r_U/r_S)$,~~

~~in which C is the concentration, in mg per mL, of USP Ketamine Related Compound A RS in the *Standard solution; W* is the weight, in mg, of Ketamine Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak responses for ketamine related compound A obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.1% of ketamine related compound A is found. In the chromatogram of the *Test solution*, the response of no other, unknown, impurity is greater than 0.3% of the ketamine peak response; and the sum of the responses of all unknown impurity peaks is not greater than 1.0% of the ketamine peak response.~~

■*Mobile phase*—Dissolve 0.95 g of sodium 1-hexanesulfonate in 1 liter of a solution consisting of a mixture of water and acetonitrile (3:1). Add 4 mL of acetic acid, and mix.

~~*Ketamine hydrochloride standard stock solution*—Dissolve an accurately weighed quantity of USP Ketamine Hydrochloride RS in *Mobile phase*, sonicating if necessary, to obtain a solution having a concentration of 1 mg per mL.~~

~~*Resolution solution*—Dissolve an accurately weighed quantity of USP Ketamine Related Compound A RS in *Mobile phase*, sonicating if necessary, to obtain a solution having a concentration of 0.5 mg per mL. To 1 mL of this solution, add 0.5 mL of *Ketamine hydrochloride standard stock solution*, and dilute with *Mobile phase* to 100 mL. [NOTE—Prepare immediately before use.]~~

Standard solution—Dissolve accurately weighed quantities of USP Ketamine Hydrochloride RS and USP Ketamine Related Compound A RS in *Mobile phase* (sonicate if necessary) to prepare a solution containing about 0.005 mg per mL of each compound. Prepare immediately before use.

Test solution—Transfer an accurately weighed quantity of about 50.0 mg of Ketamine Hydrochloride to a 50-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, sonicating if necessary. ~~Dilute 1.0 mL of the solution so obtained to 10.0 mL with *Mobile phase*. Dilute 1.0 mL of the resulting solution to 20.0 mL with *Mobile phase*.~~

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Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.0-mm × 4.0-mm guard column with a 4.0-mm × 12.5-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the ~~*Resolution solution,*~~ *Standard solution*, and record the peak responses as directed for *Procedure:* the order of elution is ketamine hydrochloride followed by ketamine related compound A; the resolution, *R*, between these two peaks is not less than 2.0; the retention time of ketamine hydrochloride is between 3.0 and 4.5 minutes (if necessary, adjust the concentration of water and acetonitrile); and the tailing factor is not greater than 1.5.

Procedure—Separately inject equal volumes (about 20 µL) of the ~~*Resolution solution,*~~ *Standard solution*, and the *Test solution* into the chromatograph, record the chromatograms, identify the ketamine hydrochloride and ketamine related compound A peaks, and measure the areas of the major peaks. Calculate the area percentage of each impurity, relative to ketamine hydrochloride, taken by the formula:

~~$100(r_i/r_u)$,~~

~~in which r_i and r_u are the peak areas of the impurity and ketamine hydrochloride, respectively, in the *Test solution*.~~

$$5000(C/W)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Ketamine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Ketamine Hydrochloride taken to prepare the *Test solution;* r_i is the peak area of each individual impurity peak in the *Test solution;* and r_S is the response of the ketamine hydrochloride peak obtained from the *Standard solution*. Not more than 0.1% of ketamine related compound A is found; the response of no other unknown impurity is greater than 0.3% of the ketamine peak area; and the sum of the responses of all unknown impurity peaks is not greater than 1.0% of the ketamine peak response.■1S (*USP27*)

Change to read:

Assay—

Buffer—Dissolve 5.75 g of monobasic ammonium phosphate in 1000 mL of water. Add 6 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and methanol (65:35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 12.5 mg each, of USP Ketamine Hydrochloride RS and USP Ketamine Related Compound A RS, both accurately weighed, to a 50-mL volumetric flask, dissolve in *Mobile phase* with the aid of sonification if necessary, dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of the solution so obtained to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard preparation—Transfer about 10 mg of USP Ketamine Hydrochloride RS, accurately weighed, to a 50-mL volumetric flask, add about 20 mL of *Mobile phase*, and sonicate to dissolve. Dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer about 20 mg of Ketamine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, add about 35 mL of *Mobile phase*, and sonicate to dissolve. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the order of elution is ketamine followed by ketamine related compound A; the resolution, *R*, between ketamine and ketamine related compound A is not less than ~~9.4;~~

■2.0;■1S (*USP27*)

the column efficiency determined from the ketamine peak is not less than 9400 theoretical plates; and the tailing factor determined from the ketamine peak is not more than 1.6. Chromatograph the *Standard preparation*, and record the ketamine peak response as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 0.6%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{13}H_{16}ClNO \cdot HCl$ in the portion of Ketamine Hydrochloride taken by the formula:

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Ketamine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the ketamine peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

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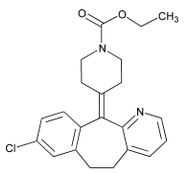
BRIEFING

Loratadine, page 1604 of *PF* 28(5) [Sept.–Oct. 2002]; **Loratadine Oral Solution,** page 1606 of *PF* 28(5) [Sept.–Oct. 2002]; **Loratadine Tablets,** page 1608 of *PF* 28(5) [Sept.–Oct. 2002]. These new monographs, which previously appeared in *Pharmacopeial Previews*, are now forwarded to *In-Process Revision* with minor editorial style changes. In the *Packaging and storage* section it is proposed to add a recommended temperature range for storage, to conform to the policy established by the USP Expert Committee on Packaging, Storage, and Distribution.

(PA1: K. Russo; PSD: C. Okeke) RTS—39761-1

Add the following:

■Loratadine



$C_{22}H_{23}ClN_2O_2$ 382.88

1-Piperidinecarboxylic acid, 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-, ethyl ester.

Ethyl 4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate [*79794-75-5*].

» Loratadine contains not less than 98.5 percent and not more than 101.0 percent of $C_{22}H_{23}ClN_2O_2$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store between 2° and 30°.

USP Reference standards ⟨11⟩—*USP Loratadine RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩.

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

Melting range ⟨741⟩: between 132° and 137°.

Loss on drying ⟨731⟩—Dry it at 100° to constant weight: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Related compounds—

Mobile phase and *Diluent*—Prepare as directed in the *Assay.*

Standard stock solution—Prepare as directed for *Standard preparation* in the *Assay.*

Standard solution—Pipet 5.0 mL of *Standard stock solution* into a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.8 µg per mL.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The column temperature is maintained between 25° and 35°. The flow rate is about 1 mL per minute. Chromatograph the *Test solution*, and record the peak areas as directed for *Procedure:* the relative retention times are about 0.79 for 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl and 1.0 for loratadine. Chromatograph the *Standard solution*, and record the peak area of the main peak as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 4.0%.

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Procedure—Separately inject equal volumes (about 50 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure all of the peak areas in the *Test solution* and the peak area of the main peak in the *Standard solution*. Calculate the percentage of each impurity in the portion of Loratadine taken by the formula:

$$10{,}000(C/F)(r_i / r_S)W,$$

in which C is the concentration, in mg per mL, of USP Loratadine RS in the *Standard solution; F* is the relative response factor for each impurity, if known, (F is 0.25 for 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl); r_i is the peak area response for each impurity in the *Test solution*; r_S is the peak area response of loratadine in the *Standard solution;* and W is the quantity, in mg, of Loratadine taken to prepare the *Test solution:* not more than 0.2% of 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl is found; not more than 0.1% of any other individual impurity is found; and not more than 0.3% of total impurities is found.

Assay—

0.01 M Dibasic potassium phosphate—Transfer about 1.74 g of anhydrous dibasic potassium phosphate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

0.6 M Dibasic potassium phosphate—Transfer 105 g of anhydrous dibasic potassium phosphate to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.01 M Dibasic potassium phosphate*, methanol, and acetonitrile (7:6:6). Adjust with 10% phosphoric acid solution to an apparent pH of 7.2. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

0.05 N Hydrochloric acid—Transfer 500 mL of water to a 1000-mL volumetric flask, add 83 mL of hydrochloric acid, dilute with water to volume, and mix. Transfer 50 mL of this solution into a 1000-mL volumetric flask, dilute with water to volume, and mix.

Diluent—Transfer 400 mL of *0.05 N Hydrochloric acid* and 80 mL of *0.6 M Dibasic potassium phosphate* to a 1000-mL volumetric flask, dilute with a mixture of methanol and acetonitrile (1:1) to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Loratadine RS in *Diluent*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.4 mg per mL.

Assay preparation—Transfer about 40 mg of Loratadine, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing 5-µm L7. The flow rate is about 1 mL per minute. The column temperature is maintained between 25° and 35°. Chromatograph the *Standard preparation*, and record the peak area responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{22}H_{23}ClN_2O_2$ in the portion of Loratadine taken by the formula:

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$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Loratadine RS in the *Standard preparation;* and r_U and r_S are the peak area responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Loratadine Oral Solution, page 1606 of *PF* 28(5) [Sept.–Oct. 2002]—See briefing under *Loratadine*.

(PA1: K. Russo; PSD: C. Okeke) RTS—39761-3

Add the following:

■Loratadine Oral Solution

» Loratadine Oral Solution contains not less than 94.0 percent and not more than 105.0 percent of the labeled amount of loratadine ($C_{22}H_{23}ClN_2O_2$).

Packaging and storage—Preserve in tight containers, and store between 2° and 30°.

USP Reference standards ⟨11⟩—*USP Loratadine RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Place a volume of Oral Solution, equivalent to about 10 mg of loratadine, in a centrifuge tube. Add 10 mL of 0.2 N sodium hydroxide and 2.0 mL of dichloromethane. Rotate for 10 minutes. Centrifuge, and discard the aqueous phase.

Standard solution—Dissolve an accurately weighed quantity of USP Loratadine RS in dichloromethane to obtain a solution having a known concentration of about 5 mg per mL.

Developing solvent system: ethyl ether and diethylamine (40:1), in a paper-lined tank.

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

Antimicrobial effectiveness test ⟨51⟩: meets the requirements.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic microbial count does not exceed 100 per mL; and the total combined molds and yeasts count does not exceed 50 cfu per mL.

Deliverable volume ⟨698⟩: meets the requirement.

pH ⟨791⟩: between 2.5 and 3.1.

Related compounds—

Mobile phase—Prepare a mixture of 15 mmol sodium dodecyl sulfate in a mixture of water and acetonitrile (1:1). Adjust with phosphoric acid to a pH of 2.6 ± 0.1, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of *Mobile phase* and water (2:1).

System suitability solution 1—Dissolve an accurately weighed quantity of USP Loratadine RS, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.002 mg per mL.

System suitability solution 2—Quantitatively transfer 5.0 mL of *System suitability solution 1* into a suitable container, dilute with *Diluent* to 50 mL, and mix.

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Resolution solution—Transfer an amount of Oral Solution, equivalent to 20 mg of loratadine, into a screw-cap, glass container. Add 1 mL of 3% aqueous hydrogen peroxide, and mix. Cap, and heat at 65° for 18 to 24 hours.

Test solution—Transfer an accurately measured volume of Oral Solution, equivalent to about 5 mg of loratadine, to a 25-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 2 mL per minute. The column temperature is maintained between 30° and 40°. Chromatograph the *Resolution solution*, and record the peak areas as directed for *Procedure:* the relative retention times are about 0.70 for ethyl 4-[8-chloro-5,6-dihydro-4-(hydroxymethyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylate, 0.84 for ethyl 4-[8-chloro-5,6-dihydro-2-(hydroxymethyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylate, and 1.0 for loratadine; and the resolution, *R*, between loratadine and ethyl 4-[8-chloro-5,6-dihydro-2-(hydroxymethyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylate is not less than 3.0. Chromatograph *System suitability solution 1*, and record the peak area response of the loratadine peak as directed for *Procedure:* the tailing factor is not less than 0.7 and not greater than 1.1. Chromatograph *System suitability solution 2*, and record the peak area response of the loratadine peak as directed for *Procedure:* the relative standard deviation for replicate injections of *System suitability solution 2* is not more than 10%.

Procedure—Inject about 50 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak area responses. Calculate the percentage of each individual related compound in the portion of Oral Solution taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the individual peak response of each related compound in the *Test solution;* and r_s is sum of the responses of all of the peaks, excluding excipient peaks: not more than 0.3% of ethyl 4-[8-chloro-5,6-dihydro-4-(hydroxymethyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylate is found; not more than 0.3% of ethyl 4-[8-chloro-5,6-dihydro-2-(hydroxymethyl)-11*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene]-1-piperidinecarboxylate is found; not more than 0.2% of any other individual impurity is found; and the sum of all impurities is not more than 0.5%.

Assay—

0.05 M Monobasic potassium phosphate solution—Transfer about 6.8 g of monobasic potassium phosphate, accurately weighed, to a 1-liter volumetric flask, dissolve in and dilute with water to volume, and mix. Adjust with phosphoric acid to a pH of 3.0 ± 0.1.

Mobile phase—Prepare a filtered and degassed mixture of *0.05 M Monobasic potassium phosphate solution* and acetonitrile (7:3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard preparation—Dissolve an accurately weighed quantity of butylparaben in a mixture of water and acetonitrile (7:3), and dilute quantitatively, and stepwise if necessary, with a mixture of water and acetonitrile (7:3) to obtain a solution having a concentration of about 0.3 mg per mL.

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Standard stock peparation—Dissolve an accurately weighed quantity of USP Loratadine RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 1.0 mg per mL.

Standard preparation—Transfer 5.0 mL of *Internal standard preparation*, 5.0 mL of *Standard stock preparation*, and 12 mL of water into a 50-mL volumetric flask. Dilute with a mixture of water and acetonitrile (7:3), and mix.

Assay preparation—Transfer an accurately measured quantity of Oral Solution, equivalent to 5 mg of loratadine, into a 50-mL volumetric flask. Pipet 5.0 mL of *Internal standard preparation* into the flask, dilute with a mixture of water and acetonitrile (7:3) to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4-mm × 30-cm column that contains 5-µm packing L11. The flow rate is about 2 mL per minute. The column temperature is maintained between 20° and 30°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.78 for butylparaben and 1.0 for loratadine; the resolution, *R*, between loratadine and butylparaben is not less than 1.9; the tailing factor is not more than 1.6 for the loratadine and butylparaben peaks; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of loratadine ($C_{22}H_{23}ClN_2O_2$) in the portion of Oral Solution taken by the formula:

$$50C(R_U / R_S),$$

in which *C* is the concentration, in mg per mL, of USP Loratadine RS in the *Standard preparation;* and R_U and R_S are the ratios of loratadine to the internal standard peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Loratadine Tablets, page 1608 of *PF* 28(5) [Sept.–Oct. 2002]—See briefing under *Loratadine.*

(PA1: K. Russo; PSD: C. Okeke) RTS—39761-2

Add the following:

■Loratadine Tablets

» Loratadine Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of loratadine ($C_{22}H_{23}ClN_2O_2$).

Packaging and storage—Preserve in ~~well closed~~ tight containers, and store between 2° and 30°. Protect from excessive moisture if packaged in blisters.

USP Reference standards ⟨11⟩—*USP Loratadine RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Transfer an accurately weighed quantity of Tablets, equivalent to about 20 mg of loratadine, to a centrifuge tube. Add 5.0 mL of a mixture of chloroform and methanol (1:1), rotate for 30 minutes, and centrifuge.

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Standard solution—Dissolve an accurately weighed quantity of about 20 mg of USP Loratadine RS in 5 mL of a mixture of chloroform and methanol (1:1), and mix.

Application volume: 5 µL.

Developing solvent system: ethyl ether and diethylamine (40:1), in a paper-lined tank.

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

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 60 minutes.

Procedure—Determine the amount of $C_{22}H_{23}ClN_2O_2$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 280 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Loratadine RS in the same *Medium*.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{22}H_{23}ClN_2O_2$ is dissolved in 60 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Related compounds—

0.01 M Dibasic potassium phosphate, *0.6 M Dibasic potassium phosphate*, *Mobile phase*, *0.05 N Hydrochloric acid*, and *Diluent*—Proceed as directed in the *Assay* under *Loratadine*.

Standard stock solution—Prepare as directed for *Standard preparation* in the *Assay* under *Loratadine*.

Standard solution—Pipet 5.0 mL of the *Standard stock solution* into a 100-mL volumetric flask, and dilute with *Diluent* to volume. Dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.8 µg per mL.

Test solution—Use the *Assay preparation*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Test solution*, and record the peak areas as directed for *Procedure:* the relative retention times are about 0.79 for 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl and 1.0 for loratadine. Chromatograph the *Standard solution*, and record the peak areas of the main peak as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure all of the peak area responses in the *Test solution* and the peak area of the main peak in the *Standard solution*. Calculate the percentage of each impurity in the portion of Tablets taken by the formula:

$$2500(C/L)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Loratadine RS in the *Standard solution; L* is the labeled quantity, in mg, of loratadine in each Tablet taken; r_i is the peak area response for each impurity in the *Test solution;* and r_S is the peak area response of loratadine in the *Standard solution:* not more than 0.2% of 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl is found; not more than 0.1% of any other individual impurity is found; and the sum of all impurities, other than 4-(8-chloro-11-fluoro-6,11-dihydro-5*H*-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-yl)-1-piperidinecarboxylate ethyl, is not more than 0.1%.

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Assay—

0.01 M Dibasic potassium phosphate, *0.6 M Dibasic potassium phosphate*, *Mobile phase*, *0.05 N Hydrochloric acid*, *Diluent*, and *Standard preparation*—Proceed as directed in the *Assay* under *Loratadine*.

Assay preparation—Transfer 10 Tablets into a 250-mL volumetric flask, add 100 mL of *0.05 N Hydrochloric acid*, and shake for 40 minutes or until the Tablets are completely disintegrated. Add 75 mL of a mixture of methanol and acetonitrile (1:1), and mix. Add 20 mL of *0.6 M Dibasic potassium phosphate*, and mix for 5 minutes. Dilute with a mixture of methanol and acetonitrile (1:1) to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay* under *Loratadine*. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 3.5; the tailing factor is not more than 1.7; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak response for the major peaks. Calculate the quantity, in mg, of $C_{22}H_{23}ClN_2O_2$ in the portion of Tablets taken by the formula:

$$250C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Loratadine RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Magnesium Oxide, *USP 26* page 1115 and page 2974 of the *First Supplement*. Because the *Labeling* section requires the indication of whether it is Light Magnesium Oxide or Heavy Magnesium Oxide, it is proposed to add the test for *Bulk density* to the monograph. Currently, the test to determine the grade of Magnesium Oxide is given only in the *Reference Tables*, under *Description and Solubility.*

(PA4: E. Gonikberg) RTS—39805-1

Add the following:

■**Bulk density,** *Method I* ⟨616⟩—Using the procedure specified in the chapter, determine the volume occupied by 25.0 g of Magnesium Oxide: the volume is approximately 200 to 250 mL for Light Magnesium Oxide, and is approximately 50 to 100 mL for Heavy Magnesium Oxide.■1S (*USP27*)

BRIEFING

Mangafodipir Trisodium, *USP 26* page 1121. Based on comments received, it is proposed to correct the unknown impurity level in the test for *Related compounds* to 0.3%, and set the limit of total impurities in the same test to 2.0%.

(RMI: A. Wilk) RTS—39859-1

Change to read:

Related compounds—

Ascorbic acid solution—Dissolve 0.4 g of ascorbic acid in 100 mL of water.

Phosphate buffer—Prepare as directed in the *Assay.*

Mobile phase—Prepare as directed in the *Assay.* [NOTE—Increasing the proportion of acetonitrile will decrease the retention times].

System suitability stock solution—Prepare as directed for *Standard stock preparation* in the *Assay.*

System suitability solution 1—Prepare a solution of USP Mangafodipir Trisodium RS having a known concentration of about 4.0 mg per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, add 5.0 mL of *System suitability stock solution*, 5.0 mL of *Phosphate buffer*, and 5.0 mL of *Ascorbic acid solution*. Dilute with nitrogen-purged water to volume, and mix to obtain a solution having a concentration of about 0.4 mg of USP Mangafodipir Trisodium RS, and about 0.01 mg each of USP Mangafodipir Related Compound A RS and USP Mangafodipir Related Compound B RS per mL. [NOTE—Store in a refrigerator and under nitrogen to avoid excessive exposure to heat, air, and light.]

System suitability solution 2—Transfer about 10 mg of USP Mangafodipir Related Compound C RS to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, and add 5.0 mL of *Phosphate buffer.*

Test solution—Transfer an accurately weighed quantity of Mangafodipir Trisodium, equivalent to about 100 mg of mangafodipir trisodium, to a 50-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a second 50-mL volumetric flask, add 5.0 mL of *Phosphate buffer*, dilute with water to volume, and mix. [NOTE—Store in a refrigerator and under nitrogen to avoid excessive exposure to heat, air, and light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph *System suitability solution 2*, and record the peak responses as directed for *Procedure:* note the elution time to identify the mangafodipir related compound C peak, if present, in the chromatogram of *System suitability solution 1.* Chromatograph *System suitability solution 1*, and record the peak responses as directed for *Procedure:* the retention time for mangafodipir is between 18 and 30 minutes. The peak area for mangafodipir related compound C is less than 0.1%. [NOTE—If the peak area is more than 0.1% of the total of all peak areas, prepare fresh quantities of *Ascorbic acid solution* and *System suitability solution 1*, and repeat the test. If the peak area of mangafodipir related compound C is still greater than 0.1%, repeat the test using another column. A contaminated column can result in oxidation of Mn(II) to Mn(III), forming related compound C.] The tailing factor for the mangafodipir peak is not more than 2.3; the column efficiency is not less than 1000 theoretical plates; the resolution, *R*, between mangafodipir related compound B and mangafodipir is not less than 1.5; and the relative standard deviation for replicate injections is not more than 10% for each peak. [NOTE—If the resolution is less than 1.5, adjust the *Mobile phase* by increasing the concentration of tetrabutylammonium hydrogen sulfate].

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for all of the major peaks. The relative retention times for ascorbic acid, mangafodipir related compound A, Mn(II)-5-methyl dipyridoxal monophosphate (Mn(II)-5-methyl DPMP) if present, mangafodipir related compound C, mangafodipir related compound B, and mangafodipir are about 0.1, 0.3, 0.4, 0.6, 0.8, and 1.0, respectively. Calculate the percentages of mangafodipir related compound A, mangafodipir related compound B, mangafodipir related compound C, and Mn(II)-5-methyl DPMP in the portion of Mangafodipir Trisodium taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak area of each impurity; and r_s is the sum of the areas of all of the peaks: not more than 0.5% each of mangafodipir related compound A and mangafodipir related compound B is found; not more than 0.6% of mangafodipir related compound C is found; not more than 0.3% of Mn(II)-5-methyl DPMP is found; not more than ~~0.1%~~

■0.3%■1S (*USP27*)
of any other impurity is found; ~~and~~

■■1S (*USP27*)
not more than a total of 0.5% of other impurities is found;

■and not more than a total of 2.0% of impurities is found.■1S (*USP27*)

BRIEFING

Mangafodipir Trisodium Injection, page 1419 of *PF* 28(5) [Sept.–Oct. 2002]. Based on the comments received, it is proposed to remove the sodium test from the *Identification* test *B*. It is also proposed to revise the Definition to correct the quantitative limits.

(RMI: A. Wilk) RTS—39549-1

Add the following:

■Mangafodipir Trisodium Injection

» Mangafodipir Trisodium Injection is a sterile solution of Mangafodipir Trisodium in Water for Injection. ~~It Each mL~~ It contains not less than ~~90.0 percent 6.81 mg 90.0 percent~~ 94.0 percent and not more than ~~110.0 percent 8.33 mg 110.0 percent~~ 106.0 percent of the labeled amount of mangafodipir trisodium ($C_{22}H_{27}MnN_4Na_3O_{14}P_2$). It may contain stabilizers and buffers. It contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose containers of Type I glass. Store at controlled room temperature, with containers on their sides in the original carton.

~~**Labeling**—Label it to indicate that the maximum dose does not exceed 15 mL.~~

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Mangafodipir Trisodium RS.*

Identification—

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

B: It meets the requirements of the tests for ~~*Sodium* ⟨191⟩ and~~ *Manganese* ⟨191⟩.

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Bacterial endotoxins ⟨85⟩: not more than 0.66 USP Endotoxin Unit per mg of mangafodipir trisodium.

pH ⟨791⟩: between 8.4 and 9.2.

Osmolarity ⟨785⟩: between 244 and 330 mOsmol per kg of water.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Phosphate buffer and *Mobile phase*—Proceed as directed in the *Assay* under *Mangafodipir Trisodium*.

Standard preparation—Prepare a solution of USP Mangafodipir Trisodium RS in water having a known concentration of about 2 mg per mL. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, add 5.0 mL of *Phosphate buffer*, dilute with water to volume, and mix. [NOTE—Store under nitrogen to avoid excessive exposure to air and light.]

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 100 mg of mangafodipir trisodium, to a 50-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, add 5.0 mL of *Phosphate buffer*, dilute with water to volume, and mix. [NOTE—Store under nitrogen to avoid excessive exposure to air and light.]

Chromatographic system—Prepare as directed in the *Assay* under *Mangafodipir Trisodium*. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the column efficiency is not less than 1000 theoretical plates; and the tailing factor is not more than 2.3.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of mangafodipir trisodium ($C_{22}H_{27}MnN_4Na_3O_{14}P_2$) in each mL of the Injection taken by the formula:

$$250(C/V)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Mangafodipir Trisodium RS in the *Standard preparation; V* is the volume, in mL, of Injection taken to prepare the *Assay preparation;* and r_U and r_S are the mangafodipir peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

BRIEFING

Mercaptopurine Tablets, *USP 26* page 1159. In accordance with the approved NDA for this product, it is proposed to replace the test for *Disintegration* with a test for *Dissolution*.

(BPC: M. Marques) RTS—37676-1

Delete the following:

■~~**Disintegration** ⟨701⟩: 30 minutes.~~ ■1S (*USP27*)

Add the following:

■**Dissolution** ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 2: 50 rpm.

Time: 60 minutes.

Determine the amount of $C_5H_4N_4S$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed solution of 0.1% acetic acid in water. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 3.9-mm × 15-cm column that contains packing

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L1. The flow rate is about 2.5 mL per minute. Chromatograph replicate injections of the Standard solution prepared as described below for *Procedure*, and record the peak responses as directed for *Procedure:* the retention time for mercaptopurine is not less than 4 minutes, and the relative standard deviation is not more than 2.0%.

Procedure—Inject a volume (about 10 µL) of a filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the quantity of $C_5H_4N_4S$ dissolved in comparison with a Standard solution having a known concentration of USP Mercaptopurine RS in the same *Medium* and similarly chromatographed.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_5H_4N_4S$ is dissolved in 60 minutes.■1S (*USP27*)

■*Standard solution*—Dissolve an accurately weighed quantity of USP Methamphetamine Hydrochloride RS in water to obtain a solution having a known concentration similar to the one expected in the *Test solution*. Dilute 2:1 with 0.15 M perchloric acid.

Test solution—Use filtered aliquots of the solution under test. Dilute 2:1 with 0.15 M perchloric acid.■1S (*USP27*)

Procedure— ~~Determine the amount of $C_{10}H_{15}N \cdot HCl$ dissolved by employing the following pressurized liquid chromatographic method. Use filtered aliquots of the solution under test diluted with 0.15 *M* perchloric acid if necessary. Prepare a Standard solution having a known concentration of USP Methamphetamine Hydrochloride RS in the same medium.~~ ■■1S (*USP27*) The liquid chromatograph is equipped with a 211-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 2.5 mL per minute. Chromatograph the *Standard solution* (about 100 µL), record the chromatogram, and measure the response for the major peak: the tailing factor is not more than 1.5, and the relative standard deviation for replicate injections is not more than 3.0%. Inject an equal volume of the ~~solution under test~~

■*Test solution*■1S (*USP27*)
into the chromatograph, record the chromatogram, and measure the response of the major peak. Calculate the quantity of $C_{10}H_{15}N \cdot HCl$ dissolved by comparison with the Standard solution.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{10}H_{15}N \cdot HCl$ is dissolved in 45 minutes.

BRIEFING

Methamphetamine Hydrochloride Tablets, *USP 26* page 1178. It is proposed to add instructions for the preparation of the *Standard solution* and *Test solution* in the *Dissolution* test.

(BPC: M. Marques) RTS—39952-1

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Change to read:

Dissolution ⟨711⟩—
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Time: 45 minutes.

■Determine the amount of $C_{10}H_{15}N \cdot HCl$ dissolved by employing the following method.■1S (*USP27*)
Mobile phase—Prepare a filtered and degassed mixture of dilute perchloric acid (1 in 20) and acetonitrile (7:3).

BRIEFING

Methenamine Hippurate Tablets, *USP 26* page 1184. In accordance with the approved NDA for this product, it is proposed to replace the test for *Disintegration* with a test for *Dissolution*.

(BPC: M. Marques) RTS—39763-1

Delete the following:

■~~**Disintegration** ⟨701⟩: 30 minutes.~~■1S (*USP27*)

Add the following:

■**Dissolution** ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 100 rpm.

Time: 30 minutes.

Standard solution—Dissolve an accurately weighed quantity of USP Methenamine Hippurate RS in water to obtain a solution having a known concentration of about 22 µg per mL.

Procedure—Determine the amount of $C_6H_{12}N_4 \cdot C_9H_9NO_3$ dissolved by employing UV absorption, using a suitable spectrophotometer, at the wavelength of maximum absorbance at about 227 nm on filtered portions of the solution under test, suitably diluted with water, if necessary, in comparison with the *Standard solution*.

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_6H_{12}N_4 \cdot C_9H_9NO_3$ is dissolved in 30 minutes.■1S (*USP27*)

BRIEFING

Miconazole Nitrate Cream, *USP 26* page 1235 and page 1302 of *PF* 26(5). Based on comments received for the *PF* 26(5) proposals, the Expert Committee has decided to resubmit the previously cancelled version with the following additional changes. The instructions for the *Standard* and *Assay preparations* are modified to incorporate these comments. The *System suitability* criteria are also expanded to include a resolution requirement. Additionally, a correction was made to the formula for the calculation of Miconazole Nitrate content, and a storage condition has been added.

(PA7b: B. Davani; PSD: C. Okeke) RTS—39875-1

Change to read:

Packaging and storage—Preserve in collapsible tubes or tight containers,

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

Change to read:

Assay—

~~*Internal standard solution*—Dissolve a suitable quantity of cholestane in a mixture of chloroform and methanol (1:1) to obtain a solution having a concentration of about 1 mg per mL.~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Miconazole Nitrate RS in methanol to obtain a solution having a known concentration of about 500 µg per mL. Transfer 10.0 mL of this solution to a test tube, and evaporate on a steam bath with the aid of a current of filtered air to dryness. Dissolve the residue in 2.0 mL of *Internal standard solution*. This *Standard preparation* has a concentration of about 2500 µg per mL.~~

~~*Assay preparation*—Transfer an accurately weighed portion of the Cream, equivalent to about 100 mg of miconazole nitrate, to a 100-mL volumetric flask. Dissolve in a mixture of isopropyl alcohol and chloroform (1:1), dilute with the same solvent mixture to volume, and mix. Pipet 25 mL of this solution into a 150-mL beaker and evaporate on a steam bath with the aid of a stream of nitrogen to dryness. Add 10 mL of chloroform to the residue, and heat on a steam bath just to boiling. Remove the beaker from the steam bath, and stir to dissolve. [NOTE—Avoid excessive evaporation of chloroform.] Add 50 mL of pentane in small portions with continuous stirring. Allow to crystallize for 10 to 15 minutes. Pass through a medium-porosity sintered-glass filter funnel with the aid of a current of air applied to the surface through a one-hole stopper fitted onto the funnel. Wash the beaker with four 5-mL portions of pentane and add the washings to the filter funnel. Wash the funnel and precipitate with four 5-mL portions of pentane. Dry the precipitate on the filter by allowing filtered air to pass through the funnel for several minutes. Dissolve the precipitate by washing the beaker and funnel with small portions of methanol, and collect the filtrate in a 50-mL volumetric flask using filtered air applied to the top of the funnel to aid in filtration. Dilute with methanol to volume, and mix. Transfer 10.0 mL of this stock solution to a test tube, and evaporate on a steam bath with the aid of a current of filtered air to dryness. Dissolve the residue in 2.0 mL of *Internal standard solution*.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 1.2-m column packed with 3% phase G32 on support S1A. The injection port, detector, and column temperatures are maintained at about 250°, 300°, and 250°, respectively, and helium is used as the carrier gas, flowing at a rate of about 50 mL per minute. The relative retention times for cholestane and miconazole nitrate are about 0.44 and 1.0, respectively. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure*: the resolution, *R*, between cholestane and miconazole nitrate is not less than 2.0; and the relative standard deviation for replicate injections is not more than 3.0%.~~

~~*Procedure*—Separately inject equal volumes (about 1 µL) of the *Assay preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$) in the portion of Cream taken by the formula:~~

$$~~0.04C(R_U/R_S)~~,$$

~~in which *C* is the concentration, in µg per mL, of USP Miconazole Nitrate RS in the *Standard preparation*; and R_U and R_S are the peak response ratios of miconazole nitrate to cholestane obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

■*Buffer solution*—Transfer 10 mL of triethylamine to a suitable flask, dilute with 1000 mL of water, adjust with phosphoric acid to a pH of about 2.5, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution*, methanol, acetonitrile, and tetrahydrofuran (8:5:4:3). Make adjustments if necessary (see *System Suitablility* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Miconazole Nitrate RS and benzoic acid in *Mobile phase*, and dilute quantitatively, and stepwise if

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necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.28 and 0.02 mg per mL for miconazole nitrate and benzoic acid, respectively.

Assay preparation—Transfer an accurately weighed quantity of Cream, equivalent to about 14 mg of miconazole nitrate, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to voulume, and mix. Sonicate in a water bath at 40° to 45° until the sample is completely dispersed, and mix. Cool the solution to below room temperature, mix, and filter a portion of the solution through a 0.45-µm teflon filter into an HPLC vial.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and 4.6-mm × 25-cm column that contains packing L11. The flow rate is about 1.0 mL per minute. The column temperature is maintained at 45°. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the column efficiency for miconazole nitrate peak is not less than 7500 theoretical plates; the tailing factor for miconazole nitrate peak is not more than 2.0; and the relative standard deviation for replicate injections of miconazole nitrate is not more than 2.0%. The resolution between miconazole nitrate and benzoic acid is not less than 13.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of miconazole nitrate ($C_{18}H_{14}Cl_4N_2O \cdot HNO_3$) in the portion of Cream taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Miconazole Nitrate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Mitomycin, *USP 26* page 1241 and page 2976 of the *First Supplement*. Revisions are proposed to establish consistency with the system of labeling adopted in 1993 by the USP Drug Nomenclature Committee (see page 5618 of *PF* 19(4) [July–Aug. 1993]). Specifically, it is now proposed to include in the monograph for this drug substance a section on labeling that would require a statement specifying that where Mitomycin is intended for use in preparing injectable dosage forms, it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed, specifying that where the label states that it is sterile, it must meet the requirements of USP general test chapter *Sterility Tests* ⟨71⟩; and where the label states that it must be subjected to further processing, it must meet the requirements of USP general test chapter *Bacterial Endotoxins Test* ⟨85⟩. It is proposed also to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA7a: W. Wright) RTS—39815-1

Change to read:

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

■Store at 25°, excursion permitted between 15° and 30°.■1S (*USP27*)

Add the following:

■**Labeling**—Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms.■1S (*USP27*)

Add the following:

■**Other requirements**—Where the label states that Mitomycin is sterile, it meets the requirements for the tests for *Sterility* and *Bacterial endotoxins* under *Mitomycin for Injection*. Where the label states that Mitomycin must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements of the test for *Bacterial endotoxins* under *Mitomycin for Injection*.■1S (*USP27*)

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BRIEFING

Mitomycin for Injection, *USP 26* page 1242. It is proposed to revise the Definition and the test for *pH* to provide standards for the injectable product with or without added matrix. Mannitol may be used as a matrix, and other suitable matrix materials may also be used. It is also proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA7a: W. Wright) RTS—39815-2

Change to read:

» Mitomycin for Injection ~~is a dry mixture of Mitomycin and Mannitol. It~~

■1S (*USP27*)
contains not less than 90.0 percent and not more than 120.0 percent of the labeled amount of $C_{15}H_{18}N_4O_5$.

Change to read:

Packaging and storage—Preserve in *Containers for Sterile Solids* as described under *Injections* ⟨1⟩, protected from light.

■Store at 25°, excursion permitted between 15° and 30°.■1S (*USP27*)

Change to read:

pH ⟨791⟩: in the solution constituted as directed in the labeling, between 6.0 and 8.0

■where it contains mannitol and between 5.5 and 8.5 where it contains hydroxypropyl betadex.■1S (*USP27*)

BRIEFING

Naltrexone Hydrochloride Tablets, *USP 26* page 1269, and page 83 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to replace the UV method in the *Dissolution* test with an HPLC procedure. The new proposed HPLC method is based on analysis performed with the NovaPak C18 brand of L1 column. The typical retention time for the naltrexone peak is about 5.7 minutes.

(BPC: M. Marques) RTS—22941-1

Change to read:

Dissolution ⟨711⟩—
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Time: 60 minutes.

Determine the amount of $C_{20}H_{23}NO_4 \cdot HCl$ dissolved ~~from UV absorbances at the wavelength of maximum absorbance at about 281 nm using filtered portions of the solution under test, diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Naltrexone RS in the same medium.~~

~~★prepared as follows. Transfer about 5.5 mg of USP Naltrexone RS to a 100 mL volumetric flask, add 1.5 mL of methanol and 0.6 mL of 0.1 N hydrochloric acid, and mix. Dilute with *Dissolution Medium* to volume, and mix.★*USP27*~~

■using the method described below.

0.05 M Buffer solution—Dissolve 7.0 g of monobasic sodium phosphate in 1 liter of water.

Mobile phase—Prepare a mixture of 600 mL of *0.05 M Buffer solution*, 1.1 g of sodium 1-octane sulfonate monohydrate and 400 mL of methanol. Adjust the pH to 6.7 ± 0.05 with dilute sodium hydroxide, if necessary, filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 3.9-mm × 15-cm column that contains packing L1 and is heated to 45°. The flow rate is about 1 mL per minute. Chromatograph replicate injections of the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative standard deviation is not more than 2.0%.

Procedure—Inject a volume (about 100 µL) of a filtered portion of the solution under test into the chromatograph, record the chromatogram, and measure the response for the major peak. Calculate the amount of $C_{20}H_{23}NO_4 \cdot HCl$ dissolved in comparison with a *Standard solution* having a known concentration of USP Naltrexone RS in the same medium and similarly chromatographed.■1S (*USP27*)

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{20}H_{23}NO_4 \cdot HCl$ is dissolved in 60 minutes.

Change to read:

Assay—
Solution A, Solution B, Mobile phase, Resolution solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Naltrexone Hydrochloride*.

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Assay preparation—Transfer not fewer than 20 Tablets to a tared container, and determine the average Tablet weight. Grind the Tablets to a homogeneous mixture. Transfer an accurately weighed portion, equivalent to about 250 mg of naltrexone hydrochloride, to a 100-mL volumetric flask. Add about 80 mL of 0.1 *M* phosphoric acid, and shake or sonicate for at least 30 minutes. Dilute with 0.1 *M* phosphoric acid to volume, mix, and filter.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Naltrexone Hydrochloride*. Calculate the quantity, in mg, of $C_{20}H_{23}NO_4 \cdot HCl$ in the portion of Tablets taken by the formula:

~~(377.86)(341.41)(100*C*)(r_U/r_S),~~

▲(377.86/341.40)100$C(r_U/r_S)$,▲*USP27*

in which the terms are defined therein.

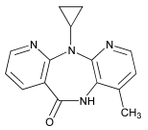
BRIEFING

Nevirapine, page 1832 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Chromatography* ⟨621⟩.

(HDQ: M. Marques) RTS—39943-4

Add the following:

■Nevirapine



$C_{15}H_{14}N_4O$ 266.30

6*H*-Dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one, 11-cyclopropyl-5,11-dihydro-4-methyl-.

11-Cyclopropyl-5,11-dihydro-4-methyl-6*H*-dipyrido[3,2-*b*:2′,3′-*e*][1,4]diazepin-6-one [*129618-40-2*].

Hemihydrate 275.31

» Nevirapine is anhydrous or contains not more than one-half molecule of water of hydration. It contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{14}N_4O$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers. Store between 15° and 30°.

Labeling—Label it to indicate whether it is anhydrous or the hemihydrate.

USP Reference standards ⟨11⟩—*USP Nevirapine Anhydrous RS. USP Nevirapine Hemihydrate RS. USP Nevirapine Related Compound A RS. USP Nevirapine Related Compound B RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—Do not dry the specimens.

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

Water, *Method I* ⟨921⟩—For anhydrous Nevirapine, proceed as directed for *Method Ic:* not more than 0.2%. For Nevirapine hemihydrate, proceed as directed for *Method Ia:* between 3.1% and 3.9%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Related compounds—

0.025 M Ammonium phosphate buffer, Mobile phase, Standard stock solution 1, Standard stock solution 2, Standard stock solution 3, and *Resolution solution*—Proceed as directed in the *Assay.*

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Standard solution—Transfer 2.0 mL of the *Standard stock solution 1* to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer an accurately weighed quantity of Nevirapine, equivalent to about 24 mg of anhydrous nevirapine, to a 100-mL volumetric flask. Add 4 mL of acetonitrile and 80 mL of *Mobile phase*, and sonicate for at least 15 minutes. Allow to cool to room temperature, dilute with *Mobile phase* to volume, and mix.

Chromatographic system—Prepare as directed in the *Assay*. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for nevirapine related compound B, 1.0 for nevirapine, and 1.5 for nevirapine related compound A; the resolution, *R*, between nevirapine related compound B and nevirapine is not less than 5.0; and the resolution between nevirapine and nevirapine related compound A is not less than 7.4. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least 80 minutes, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Nevirapine taken by the formula:

$$10{,}000(1/F)(C/W)(r_i/r_S),$$

in which F is the relative response factor for each impurity, which is equal to 1.3 for nevirapine related compound B and 1.0 for all other impurities; C is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the *Standard solution; W* is the weight of Nevirapine, in mg, taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the nevirapine peak response obtained from the *Standard solution:* not more than 0.2% each of nevirapine related compound A, nevirapine related compound B, and the impurity having a relative retention time of about 2.8 is found; not more than 0.1% of any other individual impurity is found; and not more than 0.6% of total impurities is found.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Assay—

0.025 M Ammonium phosphate buffer—Transfer 2.88 g of monobasic ammonium phosphate to a 1000-mL volumetric flask, dissolve in 800 mL of water, adjust with 1 N sodium hydroxide to a pH of about 5.0, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.025 M Ammonium phosphate buffer* and acetonitrile (4:1).

Standard stock solution 1—Transfer an accurately weighed quantity of USP Nevirapine Anhydrous RS to a volumetric flask, add a volume of a mixture of *Mobile phase* and acetonitrile (20:1), sonicate for at least 15 minutes, allow to cool to room temperature, dilute with *Mobile phase* to volume, and mix to obtain a solution having a known concentration of about 0.24 mg per mL. [NOTE—Do not use after 78 hours.]

Standard stock solution 2—Transfer an accurately weighed quantity of USP Nevirapine Related Compound A RS to a volumetric flask, add a volume of a mixture of *Mobile phase* and acetonitrile (3:1), sonicate for at least 15 minutes, allow to cool to room temperature, dilute with *Mobile phase* to volume, and mix to obtain a solution having a known concentration of about 0.24 mg per mL.

Standard stock solution 3—Transfer an accurately weighed quantity of USP Nevirapine Related Compound B RS to a volumetric flask, add a volume of a mixture of *Mobile phase* and acetonitrile (2.2:1), sonicate for at least 30 minutes, allow to cool to room temperature, dilute with *Mobile phase* to volume, and mix to obtain a solution having a known concentration of about 0.06 mg per mL.

Resolution solution—Transfer 3.0 mL of *Standard stock solution 1*, 3.0 mL of *Standard stock solution 2*, and 6.0 mL of *Standard stock solution 3* to a 25-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard preparation—Transfer 3.0 mL of *Standard stock solution 1* to a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. [NOTE—Do not use after 78 hours.]

Assay preparation—Transfer an accurately weighed quantity of Nevirapine, equivalent to about 24 mg of anhydrous nevirapine, to a 100-mL volumetric flask. Add 4 mL of acetonitrile and 80 mL of *Mobile phase*, sonicate for at least 15 minutes, allow to cool to room temperature, dilute with *Mobile phase* to volume, and mix. Transfer 3.0 mL of this solution to a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing ~~L57.~~ L## (see ⟨621⟩ *Chromatography*). The flow rate is about 1 mL per minute. The column temperature is maintained at 35°. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for nevirapine related compound B, 1.0 for nevirapine, and 1.5 for nevirapine related compound A; the resolution, *R*, between nevirapine related compound B and nevirapine is not less than 5.0; and the resolution between nevirapine and nevirapine related compound A is not less than 7.4. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{15}H_{14}N_4O$ in the portion of Nevirapine taken by the formula:

$$833.33C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Nevirapine Anhydrous RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Niacin, *USP 26* page 1304. It is proposed to change the medium in *Identification* test *B* and the *Assay* to phosphate buffer, having a pH of 7.0.

(DSN: L. Evans) RTS—39841-1

Change to read:

Identification—
A: *Infrared Absorption* ⟨197M⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 20 µg per mL.
Medium: ~~water.~~

■Use the *Buffer solution*, prepared as directed in the *Assay.*■1S (*USP27*)
Ratio: A_{237}/A_{262}, between ~~0.35 and 0.39.~~

■0.46 and 0.50.■1S (*USP27*)

In-Process Revision

Change to read:

Assay— ~~Transfer about 200 mg of Niacin, accurately weighed, to a 500-mL volumetric flask, add water to dissolve, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Concomitantly determine the absorbances of this solution and a solution of USP Niacin RS in the same medium, at a concentration of about 20 µg per mL, in 1-cm cells at the wavelength of maximum absorbance at about 262 nm, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg, of $C_6H_5NO_2$ in the Niacin taken by the formula:~~

~~$$10C(A_U/A_S),$$~~

~~in which *C* is the concentration, in µg per mL, of USP Niacin RS in the Standard solution, and A_U and A_S are the absorbances of the solution of Niacin and the Standard solution, respectively.~~

■*Buffer solution*—Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with 50% sodium hydroxide solution to a pH of 7.0.

Assay preparation—Transfer about 200 mg of Niacin, accurately weighed, to a 500-mL volumetric flask, add the *Buffer solution* to dissolve, dilute with the *Buffer solution* to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with the *Buffer solution* to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Assay preparation* and a solution of USP Niacin RS in the same medium (*Standard preparation*), at a concentration of about 20 µg per mL, in 1-cm cells at the wavelength of maximum absorbance at about 262 nm, with a suitable spectrophotometer, using the *Buffer solution* as the blank. Calculate the quantity, in mg, of $C_6H_5NO_2$ in the portion of Niacin taken by the formula:

$$10C(A_U/A_S),$$

in which *C* is the concentration, in µg per mL, of USP Niacin RS in the *Standard preparation;* and A_U and A_S are the absorbances of the solution of the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

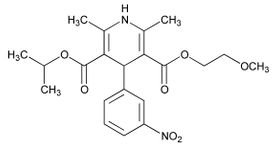
BRIEFING

Nimodipine, page 2041 of *PF* 27(1) [Jan.–Feb. 2001]. This new monograph, which previously appeared in *Pharmacopeial Previews*, is now forwarded to *In-Process Revision*.

(PA5: A. Wilk) RTS—39903-5

Add the following:

■Nimodipine



$C_{21}H_{26}N_2O_7$ 418.44

3,5-Pyridinedicarboxylic acid, 1,4-dihydro-2,6-dimethyl- 4-(3-nitrophenyl)-, 2-methoxyethyl 1-methylethyl ester.

Isopropyl 2-methoxyethyl 1,4-dihydro-2,6-dimethyl-4-(*m*-nitrophenyl)-3,5-pyridinedicarboxylate [*66085-59-4*].

» Nimodipine contains not less than 98.5 percent and not more than 101.5 percent of $C_{21}H_{26}N_2O_7$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Nimodipine RS. USP Nimodipine Related Compound A RS.*

NOTE—Throughout the following procedures, protect test or assay specimens, the Reference Standards, and solutions containing them by conducting the procedures immediately under subdued light or using low-actinic glassware.

In-Process Revision

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of *Standard solution 1*, as obtained in the test for *Chromatographic purity.*

Specific rotation ⟨781S⟩: between –10° and +10°.

Test solution: 50 mg per mL, in acetone.

Loss on drying ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Related compounds—

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, and tetrahydrofuran (3:1:1).

Standard solution 1—Transfer about 40 mg of USP Nimodipine RS, accurately weighed, to a 25-mL volumetric flask, dissolve in 2.5 mL of tetrahydrofuran, dilute with *Mobile phase* to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 2.0 mL of this second solution to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard solution 2—Transfer about 20.0 mg of USP Nimodipine Related Compound A RS, accurately weighed, to a 25-mL volumetric flask, dissolve in 2.5 mL of tetrahydrofuran, dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard solution 3—Transfer 2.5 mL of *Standard solution 1* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard solution 4—Transfer 1.0 mL of *Standard solution 2* and 1.0 mL of *Standard solution 3* to a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer about 40 mg of Nimodipine, accurately weighed, to a 25-mL volumetric flask, dissolve in 2.5 mL of tetrahydrofuran, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 4.6-mm × 12.5-cm column that contains packing L1. The flow rate is about 2 mL per minute. The column temperature is maintained at 40°. Chromatograph *Standard solution 4*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for nimodipine related compound A and 1.0 for nimodipine; the resolution, *R*, between nimodipine related compound A and nimodipine is not less than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of *Standard solution 1*, *Standard solution 4*, and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. [NOTE—Record the chromatogram of the *Test solution* for a period of time equivalent to four times the retention time of nimodipine.] Calculate the percentage of each impurity in the portion of Nimodipine taken by the formula:

$$100C(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Nimodipine Related Compound A RS in *Standard solution 4;* r_i is the peak response of each impurity obtained from the *Test solution;* and r_S is the peak response of nimodipine related compound A obtained from *Standard solution 4:* not more than 0.1% of nimodipine related compound A is found; not more than 0.2% of any other individual impurity is found; and not more than 0.5% of total impurities is found.

In-Process Revision

Assay—Transfer about 180 mg of Nimodipine, accurately weighed, to a 100-mL beaker. Dissolve, with gentle heating, by stirring in a mixture of 25 mL of tertiary butyl alcohol and 25 mL of perchloric acid TS. Add 0.1 mL of ferroin TS. Titrate with 0.1 N ceric sulfate VS. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N ceric sulfate is equivalent to 20.92 mg of $C_{21}H_{26}N_2O_7$.■1S (*USP27*)

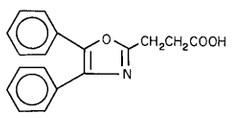
BRIEFING

Oxaprozin, page 97 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to add drying conditions for the sample in *Identification* test *B*.

(PA2: J. Kelly) RTS—39081-1

Add the following:

■Oxaprozin



$C_{18}H_{15}NO_3$ 293.32

2-Oxazolepropanoic acid, 4,5-diphenyl-.

4,5-Diphenyl-2-oxazolepropionic acid [*21256-18-8*].

» Oxaprozin contains not less than 98.5 percent and not more than 101.5 percent of $C_{18}H_{15}NO_3$, calculated on the dried basis.

NOTE—Because of light sensitivity, protect all oxaprozin samples and Standard solutions from light.

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

USP Reference standards ⟨11⟩—*USP Oxaprozin RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩: previously dried at 105° for 2 hours.

B: *Ultraviolet Absorption* ⟨197U⟩: previously dried at 105° for 2 hours.

Solution: 10 µg per mL.

Medium: methanol. ~~The absorption of the sample~~ Absorptivity at 285 nm is between 45.5 and 49.5.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.3% of its weight.

Residue on ignition ⟨281⟩: not more than 0.3%.

Arsenic, *Method II* ⟨211⟩: 1 µg per g.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Chromatographic purity—

Solution A: 0.1% phosphoric acid adjusted with phosphoric acid to a pH of 2.00 ± 0.1.

Solution B: acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent A: a mixture of acetonitrile, methylene chloride, and water (48:1:1).

Diluent B: a mixture of acetonitrile and water (1:1).

Standard stock solution—Dissolve an accurately weighed quantity of USP Oxaprozin RS in acetonitrile to obtain a solution having a concentration of about 200 µg per mL.

In-Process Revision

Standard solution—Transfer 5.0 mL of *Standard stock solution* to a 200-mL volumetric flask, and dilute with *Diluent A* to volume.

Benzil solution: 200 µg of benzil per mL in acetonitrile.

Resolution solution—Transfer 5.0 mL of *Benzil solution* and 5.0 mL of *Standard stock solution* to a 100-mL volumetric flask, and dilute with *Diluent A* to volume to obtain a solution having known concentrations of about 10 µg of each per mL.

Test solution A—[NOTE—*Test solution A* is used to monitor all known and unknown impurities, except imidazolic acid and oximide.] Transfer about 100 mg of Oxaprozin, accurately weighed, to a 100-mL volumetric flask, add 2 mL of methylene chloride, 2 mL of water, and 75 mL of acetonitrile, and sonicate after each solvent is added. Dilute with acetonitrile to volume.

Test solution B—[NOTE—*Test solution B* is used to monitor only imidazolic acid and oximide.] Transfer about 100 mg of Oxaprozin, accurately weighed, to a 100-mL volumetric flask, add 75 mL of *Diluent B* to dissolve the Oxaprozin, and dilute with *Diluent B* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 238-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is 1.0 mL per minute. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	70	30	equilibration
0–20	70	30	isocratic
21–60	70→0	30→100	linear gradient
60–61	0→70	100→30	linear gradient
61–70	70	30	isocratic

Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 1.1 for benzil and 1.0 for oxaprozin; and the resolution, *R*, between oxaprozin and benzil is not less than 3.0. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 5.0 %.

Procedure—Inject 20 µL of *Test solution A* and *Test solution B* into the chromatograph, record the chromatogram, and measure the areas for all the peaks. Calculate the percentage of each impurity in the portion of Oxaprozin taken by the formula:

$$100(Fr_i / r_s),$$

in which F is the relative response factor and is equal to 1.15 for ~~any~~ the imidazolic acid peak with a relative retention time of 0.14, 1.21 for any peak with a relative retention time of 0.42, 0.91 for ~~any~~ the oximide peak with a relative retention time of 0.73, 0.85 for any peak with a relative retention time of 0.84, 1.29 for any peak with a relative retention time of 1.08, 1.46 for any peak with a relative retention time of 1.50, and 2.09 for any peak with a relative retention time of 1.57; ~~and 1.0 for the oxaprozin peak~~ r_i is the peak response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 0.1% of any impurity is found; not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found. [NOTE—The values of F for all known impurities except imidazolic acid and oximide were found using *Test solution A*, and the values of F for imidazolic acid and oximide were found using *Test solution B*.]

Organic volatile impurities, *Method V* ⟨467⟩: meets the requirements.

Solvent: dimethyl sulfoxide.

In-Process Revision

Assay—Dissolve about 400 mg of Oxaprozin, previously dried at 105° for 2 hours and accurately weighed, in about 100 mL of alcohol in a narrow-mouth container, and titrate with 0.1 N sodium hydroxide VS, determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N sodium hydroxide is equivalent to 29.332 mg of oxaprozin.■1S (*USP27*)

BRIEFING

Oxaprozin Tablets, page 99 of *PF* 29(1) [Jan.–Feb. 2003]. The phrase ''calculated on the dried basis'' is editorially removed from the Definition of this newly proposed monograph.

(PA2: J. Kelly) RTS—39796-1

Add the following:

■Oxaprozin Tablets

» Oxaprozin Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of oxaprozin ($C_{18}H_{15}NO_3$).~~, calculated on the dried basis.~~

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

USP Reference standards ⟨11⟩—*USP Oxaprozin RS.*

NOTE—Because of light sensitivity, protect all oxaprozin samples and Standard solutions from light.

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution: 2 mg per mL of oxaprozin in acetone.

Developing solvent system: a mixture of ethyl acetate and glacial acetic acid (99:1).

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

Dissolution ⟨711⟩—

Medium: 0.05 M monobasic potassium phosphate buffer, pH 7.4; 1000 mL.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_{18}H_{15}NO_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 286 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Oxaprozin RS in the same *Medium* (an amount of methanol not exceeding 5% of the final volume can be added to help solubilize the Reference Standard).

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{18}H_{15}NO_3$ is dissolved in 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Water, *Method Ia* ⟨921⟩: not more than 3.5%.

Assay—

0.1% Phosphoric acid, pH 2.00 ± 0.10—Add concentrated phosphoric acid, dropwise, to water to obtain a pH of 2.00 ± 0.10.

Mobile phase—Prepare a filtered and degassed solution of *0.1% Phosphoric acid, pH 2.00 ± 0.10* and acetonitrile (55:45).

Standard preparation—Dissolve an accurately weighed quantity of USP Oxaprozin RS in acetonitrile to obtain a solution having a concentration of about 12 µg of oxaprozin per mL.

In-Process Revision

Assay stock preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of oxaprozin, to a 100-mL volumetric flask, add about 10 mL of water, and sonicate for 10 minutes. Add about 40 mL of acetonitrile, sonicate for 30 minutes, shake by mechanical means for an additional 30 minutes, add about 30 mL of acetonitrile, and sonicate for 10 minutes. Dilute with acetonitrile to volume.

Assay preparation—Quantitatively dilute the *Assay stock preparation* with acetonitrile to obtain a solution having a concentration of about 12 µg of oxaprozin per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of oxaprozin ($C_{18}H_{15}NO_3$) in the portion of Tablets taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration in mg per mL of USP Oxaprozin RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

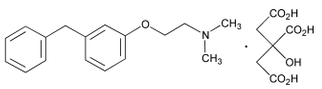
BRIEFING

Phenyltoloxamine Dihydrogen Citrate, page 428 of *PF* 29(2) [Mar.–Apr. 2003]. Because *Identification* test *A* is sufficient for distinguishing between the citrate form and the phenyltoloxamine base, and because *Identification* test *B* cannot discriminate the citrate salt from the phenyltoloxamine base and 2-benzylphenol (starting material), it is proposed to delete both *Identification* tests *B* and *C*. Several modifications to *Related compounds* are also proposed: in the preparation of the *Resolution solution*, replacing the extraction solvent, ethyl ether, and the reconstitution solvent, chloroform, with methylene chloride; and changing the sample weight from 800 mg to 400 mg in order for the peak response to be within the linear range of the HPLC detector. It is also proposed to (1) change the resolution criterion from not less than 2.0 to not less than 1.5 to meet *System suitability* requirements while maintaining sufficient resolution between the peaks; (2) revise the limit of phenyltoloxamine dihydrogen citrate related compound A to 0.2%; and (3) clarify the limit for other impurities.

(PA1: K. Russo) RTS—37538-1; 39771-1

Add the following:

■Phenyltoloxamine Dihydrogen Citrate



$C_{17}H_{21}NO \cdot C_6H_8O_7$ 447.47

N,*N*-Dimethyl-2-(α-phenyl-*o*-tolyloxy)ethylamine, citrate (1:1) salt.

2-(2-Dimethylaminoethoxy)diphenylmethane, citrate (1:1) salt [*1176-08-5*].

» Phenyltoloxamine Dihydrogen Citrate contains not less than 99.0 percent and not more than 101.0 percent of $C_{17}H_{21}NO \cdot C_6H_8O_7$, calculated on the dried basis.

Packaging and storage—~~Preserve in well-closed containers.~~ Preserve in well-closed containers and store at room temperature.

USP Reference standards ⟨11⟩—*USP Phenyltoloxamine Dihydrogen Citrate RS. USP Phenyltoloxamine Dihydrogen Citrate Related Compound A RS.*

In-Process Revision

Identification—

~~**A:** *Infrared Absorption* ⟨197K⟩.~~

~~**B:** *Ultraviolet Absorption* ⟨197U⟩—~~

~~*Solution:* 100 µg per mL.~~

~~*Medium:* 0.1 N hydrochloric acid.~~

~~**C:** Dissolve 0.5 g of Phenyltoloxamine Dihydrogen Citrate in 15 mL of hot water, add a slight excess of 5 M sodium hydroxide, filter, and add 2 N hydrochloric acid until the filtrate is neutral to litmus paper: the solution meets the requirements of the test for *Citrate* ⟨191⟩.~~, *Infrared Absorption* ⟨197K⟩.

Melting range, *Class 1a* ⟨741⟩: between 137° and 143°.

pH ⟨791⟩: between 3.2 and 4.2, in a solution (1 in 100).

Loss on drying ⟨731⟩—Dry it in vacuum at 80° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method I* ⟨231⟩: 20 µg per g.

Related compounds—

Resolution solution—In a separatory funnel dissolve about 10 mg each of USP Phenyltoloxamine Dihydrogen Citrate RS and USP Phenyltoloxamine Dihydrogen Citrate Related Compound A RS, accurately weighed, in 50 mL of water. Add 5 mL of ammonium hydroxide, and extract with three 10-mL portions of ~~ethyl ether~~ methylene chloride. Combine the extracts, dry the solution over anhydrous sodium sulfate, and gently evaporate to dryness. Dissolve the residue in 20 mL of ~~chloroform~~ methylene chloride.

Test solution—In a separatory funnel dissolve about ~~800 mg~~ 400 mg of Phenyltoloxamine Dihydrogen Citrate, accurately weighed, in 50 mL of water. Proceed as directed for *Resolution solution*, beginning with "Add 5 mL of ammonium hydroxide."

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a split injection system, a flame-ionization detector, and a 0.32-mm × 25-m column coated with a 0.45-µm film of phase G27. The carrier gas is helium, flowing at a rate of about 29 cm per second, with a split flow rate of about 25 mL per minute. The column temperature is programmed as follows. Initially the temperature of the column is equilibrated at 190° for 3 minutes, then the temperature is increased at a rate of 4° per minute to 240°, and maintained at 240° for 8 minutes. The injection port and the detector temperatures are maintained at 280°. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between phenyltoloxamine dihydrogen citrate and phenyltoloxamine dihydrogen citrate related compound A is not less than ~~2.0~~ 1.5.

Procedure—Inject a volume (about 1 µL) of the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Phenyltoloxamine Dihydrogen Citrate taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response of each impurity; and r_s is the sum of the responses of all the peaks, excluding the solvent peaks: not more than 0.2% of phenyltoloxamine dihydrogen citrate related compound A; not more than 0.1% of any other individual impurity; ~~is found;~~ and not more than 1.0% of total impurities is found.

Organic volatile impurities, *Method 1* ⟨467⟩: meets the requirements.

Assay—Dissolve about 0.5 g of Phenyltoloxamine Dihydrogen Citrate, accurately weighed, in 80 mL of glacial acetic acid, and titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid is equivalent to 44.75 mg of $C_{17}H_{21}NO \cdot C_6H_8O_7$. ■1S (*USP27*)

In-Process Revision

BRIEFING

Potassium Chloride, *USP 26* page 1502. It is proposed to revise the test for *Iodide or bromide* to include standard solutions of known concentrations for comparison purposes. The proposed procedure includes (1) a *Standard solution* for *Iodide* and a limit of 0.005% iodide that represents the visual detection limit and (2) a *Standard solution* for *Bromide* with a limit of 0.1% bromide that corresponds to the EP monograph for potassium chloride. It is proposed to use a chloramine T solution instead of chlorine TS to affect color development. Also, it is proposed to revise the *Packaging and storage* statement to include the recommended storage at up to 25 ± 2°, in accordance with the policy established by the USP Packaging, Storage, and Distribution Expert Committee.

(PA1: K. Russo; PSD: C. Okeke) RTS—38376-1; 39870-2

Change to read:

Packaging and storage—Preserve in well-closed containers, ■and store at up to 25 ± 2°.■1S (*USP27*)

Change to read:

Iodide or bromide— ~~Dissolve 2 g in 6 mL of water, add 1 mL of chloroform, and then add, dropwise, with constant agitation, 5 mL of a mixture of equal parts of chlorine TS and water: the chloroform is free from even a transient violet or a permanent orange color.~~

■IODIDE—

Standard stock solution—Transfer an accurately weighed quantity, about 41 mg, of potassium iodide to a 25-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Standard solution—Dilute 1.0 mL of *Standard stock solution* with water to 25 mL, and mix. Dilute 2.0 mL of this solution with water to 8 mL, and proceed as directed for *Test solution* beginning with "Add 1 mL each of chloroform . . .".

Test solution—Dissolve 2 g of Potassium Chloride in 8 mL of water. Add 1 mL each of chloroform and diluted hydrochloric acid, then add 2 drops of a chloramine T solution (0.1 in 100), and shake gently. The violet color of the chloroform layer is not darker than that of a concomitantly prepared *Standard solution:* the limit is 0.005%.

BROMIDE—

Standard solution—Transfer an accurately weighed quantity, about 32 mg, of sodium bromide to a 25-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. Dilute 2.0 mL of this solution with water to 8 mL, and proceed as directed for *Test solution* beginning with "Add 1 mL each of chloroform . . .".

Test solution—Dissolve 2 g of Potassium Chloride in 8 mL of water. Add 1 mL each of chloroform and diluted hydrochloric acid, then add 5 drops of a chloramine T solution (1 in 100), and shake gently. The brown color of the chloroform layer is not darker than that of a concomitantly prepared *Standard solution:* the limit is 0.1%.■1S (*USP27*)

BRIEFING

Povidone, *USP 26* page 1519. On the basis of comments received, it is proposed to revise the Definition for clarification. Also, in the test for *Limit of aldehydes*, on the basis of reported problems with the solubility in *Phosphate buffer* of Povidones with K-values greater than 90, it is proposed to change the concentration of potassium pyrophosphate in the buffer from 50 g per 500 mL to 8.3 g per 500 mL. All Povidone types categorized by K-values are known to be soluble at room temperature at the lower buffer concentration.

(EMC: C. Sheehan; D. Bempong) RTS—39648-1

Change to read:

» Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. ~~It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10 to 120. The K-value of Povidone having a nominal K-value of 15 or less is not less than 85.0 percent and not more than 115.0 percent of the nominal K-value, and K-value of Povidone having a nominal K-value or nominal K-value range with an average of more than 15 is not less than 90.0 percent and not more than 108.0 percent of the nominal K-value or average of the nominal K-value range.~~

In-Process Revision

■The different types of Povidone are characterized by their viscosity in aqueous solution, relative to that of water, expressed as a K-value. (See the section on *K-value* below.) The K-value of Povidone having a stated (nominal) K-value of 15 or less is not less than 85.0 percent and not more than 115.0 percent of the stated values. The K-value of Povidone having a stated K-value or a stated K-value range with an average of more than 15 is not less than 90.0 percent and not more than 108.0 percent of the stated value or of the average of the stated range.■1S (*USP27*)

Change to read:

Limit of aldehydes—

Phosphate buffer—Transfer ~~50.0 g~~

■8.3 g■1S (*USP27*) of potassium pyrophosphate to a 500-mL volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N hydrochloric acid to a pH of 9.0, dilute with water to volume, and mix.

Aldehyde dehydrogenase solution—Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, dissolve in 10.0 mL of water, and mix. [NOTE—This solution is stable for 8 hours at 4°.]

NAD solution—Transfer 40 mg of nicotinamide adenine dinucleotide to a glass vial, dissolve in 10.0 mL of *Phosphate buffer*, and mix. [NOTE—This solution is stable for 4 weeks at 4°.]

Standard preparation—Add about 2 mL of water to a glass weighing bottle, and weigh accurately. Add about 100 mg (about 0.13 mL) of freshly distilled acetaldehyde, and weigh accurately. Transfer this solution to a 100-mL volumetric flask. Rinse the weighing bottle with several portions of water, transferring each rinsing to the 100-mL volumetric flask. Dilute the solution in the 100-mL volumetric flask with water to volume, and mix. Store at 4° for about 20 hours. Pipet 1 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

Test preparation—Transfer about 2 g of Povidone, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Phosphate buffer*, dilute with *Phosphate buffer* to volume, and mix. Insert a stopper into the flask, heat at 60° for 1 hour, and cool to room temperature.

Procedure—Pipet 0.5 mL each of the *Standard preparation*, the *Test preparation*, and water to provide the reagent blank into separate 1-cm cells. Add 2.5 mL of *Phosphate buffer* and 0.2 mL of *NAD solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2 to 3 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Add 0.05 mL of *Aldehyde dehydrogenase solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Calculate the percentage of aldehydes, expressed as acetaldehyde, in the portion of Povidone taken by the formula:

$$10(C/W)\left[\frac{(A_{U2}-A_{U1})-(A_{B2}-A_{B1})}{(A_{S2}-A_{S1})-(A_{B2}-A_{B1})}\right],$$

in which C is the concentration, in mg per mL, of acetaldehyde in the *Standard preparation; W* is the weight, in g, of Povidone taken; A_{U1}, A_{S1}, and A_{B1} are the absorbances of the solutions obtained from the *Test preparation*, the *Standard preparation*, and the water reagent blank, respectively, before addition of the *Aldehyde dehydrogenase solution;* and A_{U2}, A_{S2}, and A_{B2} are the absorbances of the solutions obtained from the *Test preparation*, the *Standard preparation*, and the water reagent blank, respectively, after addition of the *Aldehyde dehydrogenase solution:* not more than 0.05% is found.

BRIEFING

Protamine Sulfate Injection, *USP 26* page 1586. On the basis of comments and stability data received, it is proposed to revise the *Packaging and storage* section to change the specified storage temperature from refrigerator conditions to controlled room temperature. Interested parties are encouraged to submit comments to the Expert Committee on Packaging, Storage, and Distribution.

(PSD: C. Okeke; BNT: I. DeVeau) RTS—33844-1

Change to read:

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass. Store ~~in a refrigerator.~~

■at controlled room temperature.■1S (*USP27*)

BRIEFING

Pseudoephedrine Hydrochloride Extended-Release Tablets, *USP 26* page 1591 and page 110 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to separate the *Drug release* tests according to the dosing, 12 and 24 hours. Also, in accordance with the approved supplement to the NDA, it is proposed to modify the *Tolerances* in *Drug release Test 2* from "not less than 90%" to "not less than

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85%". In the absence of any significant adverse comment, it is proposed to implement this revision via the *Sixth Interim Revision Announcement* pertaining to *USP 26–NF 21*, with an official date of December 1, 2003.

(BPC: M. Marques) RTS—39898-1

Change to read:

» Pseudoephedrine Hydrochloride Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ▪pseudoephedrine hydrochloride▪2S (*USP26*) ($C_{10}H_{15}NO \cdot HCl$).

Add the following:

•**Labeling**—When more than one *Drug Release* test is given, the labeling states the *Drug Release* test used only if *Test 1* is not used.•6

Add the following:

•**Drug release** ⟨724⟩—

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

Test 1:

Medium: water; 900 mL.

Apparatus 2: 50 rpm

Times: 1, 3, and 6 hours.

Standard solution—Dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.13 mg per mL.

Procedure—Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved by employing the procedure set forth in the *Assay*. Separately inject equal volumes (about 50 µL) of the *Standard solution* and the filtered solution under test. Calculate the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved per Tablet.

Times and Tolerances:

Time (hours)	Amount dissolved
1	between 25% and 45%
3	between 50% and 75%
6	not less than 75%

Test 3: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3*.

Medium, *Apparatus*, and *Times*—Proceed as directed for *Test 1*.

Procedure—Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 214 nm on portions of the solution under test, filtered through a 0.45-µm filter and suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Pseudoephedrine Hydrochloride RS in the same *Medium*.

Times and Tolerances:

Time (hours)	Amount dissolved
1	between 25% and 45%
3	between 60% and 80%
6	not less than 80%

FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2*.

Medium: 0.9% sodium chloride in water; 50 mL.

Apparatus 7: 30 cycles per minute; 2–3 cm amplitude. To prepare the sample, see *Figure 1* below that illustrates the following steps:

1. Place one Tablet on a 5- × 5-cm nylon netting.
2. Fold netting over the Tablet. Continue folding until the Tablet is enclosed in netting.

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3. Fold netting so that the two open ends meet. The Tablet should be enveloped in the center of the netting.
4. Insert rod (see *Figure 7c* under *Drug Release* ⟨724⟩) through netting to secure the Tablet.
5. Secure netting with HPLC plastic ferrules or other appropriate device. Trim the excess netting. Attach each sample holder to the vertically reciprocating sample holder.

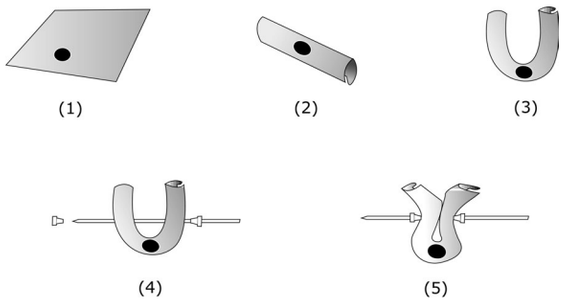

Fig. 1

Times: 2, 8, 14, and 24 hours.

Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved by employing the following method.

0.05 M Phosphate buffer, pH 6.8—Transfer 200 mL of water to a 1000-mL volumetric flask. Add 3.4 mL of phosphoric acid and 5 mL of triethylamine. Add water to almost 900 mL. Adjust with 1 N sodium hydroxide to a pH of about 6.8, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.05 M Phosphate buffer, pH 6.8* and methanol (9:1).

System suitability solution—Dissolve an accurately weighed quantity of USP Pseudoephedrine RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.4 mg per mL.

Standard solutions—Prepare solutions in water having accurately known concentrations of USP Pseudoephedrine Hydrochloride RS in a range around the expected concentration of the solution under test at each time interval.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the tailing factor for the analyte peak is not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solutions* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peak. Construct a calibration curve by plotting the peak response versus concentration of the *Standard solutions*. Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at each time interval from a linear regression analysis of the calibration curve.

Times and Tolerances:

Time (hours)	Amount dissolved
2	between 20% and 35%
8	between 40% and 65%
14	between 60% and 90%
24	not less than ~~90%~~ 85%●6

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of alcohol and ammonium acetate solution (1 in 250) (17:3).

Standard preparation—Dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in alcohol to obtain a solution having a known concentration of about 1.2 mg per mL.

Assay preparation—Transfer not fewer than 20 Tablets to a suitable container, add 500 mL of alcohol, and homogenize until the Tablets are dispersed. Quantitatively transfer the contents of the container to a 1000-mL volumetric flask, dilute with alcohol to volume, mix, and allow to stand for solids to settle. Transfer 25.0 mL of the supernatant into a 50-mL volumetric flask, dilute with alcohol to volume, and mix.

■Pass a portion of this solution through a 0.45-µm filter before injection.■2S *(USP26)*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains packing L3. The flow rate is about 0.7 mL per minute. Chromatograph the *Standard prepa-*

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ration, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of pseudoephedrine hydrochloride ($C_{10}H_{15}NO \cdot HCl$) in the portion of Tablets taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Pseudoephedrine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

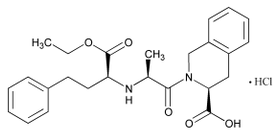
BRIEFING

Quinapril Hydrochloride, page 8429 of *PF* 25(4) [July–Aug. 1999]; **Quinapril Tablets,** page 8432 of *PF* 25(4) [July–Aug. 1999]. These new monographs, which previously appeared in *Pharmacopeial Previews*, are now being forwarded with minor editorial revisions to *In-Process Revision*. The molecular weight of quinapril hydrochloride is revised to reflect the current atomic weight values published in *USP 26*.

(PA5: A. Wilk) RTS—39894-1

Add the following:

■Quinapril Hydrochloride



$C_{25}H_{30}N_2O_5 \cdot HCl$ ~~474.99~~ 474.98

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1, 2,3,4-tetrahydro-, monohydrochloride, [3*S*-[2 [*R**(*R**)],3*R**]].

(*S*)-2-[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride [*82586-55-8*].

» Quinapril Hydrochloride contains not less than 98.5 percent and not more than 101.5 percent of $C_{25}H_{30}N_2O_5 \cdot HCl$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Quinapril Hydrochloride RS. USP Quinapril Related Compound A RS. USP Quinapril Related Compound B RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Specific rotation ⟨781S⟩: between +14.4° and +15.4°.

Test solution: 20 mg per mL, in methanol.

Water, *Method I* ⟨921⟩: not more than 1.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Limit of residual solvents—

Standard stock solution—Transfer about 50 mL of dimethylformamide to a 200-mL volumetric flask. Add about 75 mg each of acetone and acetonitrile and 30 mg each of methylene chloride and toluene, each accurately weighed by difference, and mix. Dilute with dimethylformamide to volume, and mix.

System suitability solution 1—Transfer about 25 mL of dimethylformamide to a 50-mL volumetric flask. Add 35 µL of dehydrated alcohol and 25 µL of methylene chloride. Dilute with dimethylformamide to volume, and mix. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, dilute with dimethylformamide to volume, and mix.

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System suitability solution 2—Transfer 2.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with dimethylformamide to volume, and mix.

Standard solution—Transfer 4.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with dimethylformamide to volume, and mix.

Test solution—Transfer about 60 mg of Quinapril Hydrochloride, accurately weighed, to a suitable headspace vial, add 5.0 mL of dimethylformamide, seal, and shake to dissolve.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a headspace sampler, a 0.53-mm × 30-m fused-silica column coated with a 1.0-µm film of phase G16, and a split injection system. The carrier gas is helium, flowing at a rate of 6 mL per minute. The split flow rate is about 100 mL per minute, with a back pressure of 3.5 psi. The oven temperature of the headspace sampler is maintained at 60°, and the vial pressure is maintained at 6.1 psi. The temperature of the headspace loop and transfer lines is maintained at 65°. The vials are equilibrated for 10 minutes prior to injection, and injection occurs every 36 minutes. The chromatograph is programmed as follows. Initially the column temperature is maintained at 35° for 10 minutes, then the temperature is increased at a rate of 7° per minute to 150°, and maintained at 150° for 4 minutes. The injection port temperature is maintained at 180°, and the detector is maintained at 240°. Chromatograph *System suitability solution 1*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.94 for methylene chloride and 1.0 for alcohol; the resolution, *R*, between methylene chloride and alcohol is not less than 1.2; the column efficiency, determined from the methylene chloride peak, is not less than 4900 theoretical plates; and the tailing factor for the methylene chloride peak is not more than 1.7. Chromatograph *System suitability solution 2*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 15.0%.

Procedure—Separately inject equal volumes (about 1 mL) of the gaseous headspace of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the percentages, by weight, of acetone, acetonitrile, methylene chloride, and toluene in the portion of Quinapril Hydrochloride taken by the formula:

$$0.2(W_S / W_Q)(r_U / r_S),$$

in which W_S is the weight, in mg, of the appropriate solvent taken to prepare the *Standard solution;* W_Q is the weight, in mg, of Quinapril Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak responses of the relevant solvent obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.25% each of acetone and acetonitrile is found; and not more than 0.1% each of methylene chloride and toluene is found.

Related compounds—

Diluent, *Mobile phase*, and *Chromatographic system*—Prepare as directed in the *Assay.*

System suitability solution—Prepare as directed for the *System suitability preparation* in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS in *Diluent* to obtain a solution having known concentrations of about 0.5 mg of each per mL. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of each quinapril related compound in the portion of Quinapril Hydrochloride taken by the formula:

$$100(V_U / W_U)C_S(r_U / r_S),$$

in which V_U is the volume, in mL, of the *Test solution;* W_U is the weight, in mg, of Quinapril Hydrochloride taken to prepare the *Test solution;* C_S is the concentration, in mg per mL, of the relevant USP Reference Standard in the *Standard solution;* and r_U and r_S are the peak areas of the corresponding quinapril related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% each of quinapril related compound A and quinapril related compound B is found. Calculate the percentage of each impurity in the portion of Quinapril Hydrochloride taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the sum of the responses of all the peaks obtained from the *Test solution:* not more than 0.2% of any individual impurity, other than quinapril related compound A and quinapril related compound B, is found; and not more than 2.0% of total impurities is found.

Content of chloride—Transfer about 100 mg of Quinapril Hydrochloride, accurately weighed, to a 100-mL beaker. Dissolve in 50 mL of water and 10 mL of alcohol. Acidify with nitric acid. Titrate with 0.01 N silver nitrate VS, and determine the endpoint potentiometrically, using suitable electrodes (see *Titrimetry* ⟨541⟩). Perform a blank determination, and make any necessary correction. Each mL of 0.01 N silver nitrate is equivalent to 0.3545 mg of chloride: not less than 7.2% and not more than 7.6% of chloride is found.

Assay—

Diluent—Prepare a mixture of pH 6.5, 0.025 M monobasic ammonium phosphate solution and acetonitrile (3:2).

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and methanesulfonic acid (72:28:0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability preparation—Dissolve accurately weighed quantities of USP Quinapril Hydrochloride RS, USP Quinapril Related Compound A RS, and USP Quinapril Related Compound B RS in *Diluent* to obtain a solution having known concentrations of about 2 mg of USP Quinapril Hydrochloride RS per mL and 0.005 mg each of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Quinapril Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 2 mg per mL.

Assay preparation—Transfer about 100 mg of Quinapril Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector, a 4.6-mm × 3-cm guard column that contains 5-µm packing L10, and a 4.6-mm × 25-cm column that contains 5-µm packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability preparation*, and record the peak responses as directed for *Procedure:* the resolution between quinapril and quinapril related compound A is not less than 1.75; the resolution between quinapril and quinapril related compound B is not less than 3.5;

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the column efficiency is not less than 550 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the quinapril hydrochloride peaks. Calculate the quantity, in mg, of $C_{25}H_{30}N_2O_5 \cdot HCl$ in the portion of Quinapril Hydrochloride taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Quinapril Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Quinapril Tablets, page 8432 of *PF* 25(4) [July–Aug. 1999]—See briefing under *Quinapril Hydrochloride*.

(PA5: A. Wilk) RTS—39894-2

Add the following:

■Quinapril Tablets

» Quinapril Tablets contain an amount of Quinapril Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of quinapril ($C_{25}H_{30}N_2O_5$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Quinapril Hydrochloride RS. USP Quinapril Related Compound A RS. USP Quinapril Related Compound B RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Transfer a quantity of finely powdered Tablets, equivalent to about 10.0 mg of quinapril, to a 15-mL centrifuge tube, add 5 mL of methanol, mix, and centrifuge for 10 minutes.

Standard solution—Transfer about 10.8 mg of USP Quinapril Hydrochloride RS to a 15-mL centrifuge tube, add 5 mL of methanol, mix, and centrifuge for 10 minutes.

Application volume: 25 µL.

Developing solvent system: a mixture of methanol and ethyl acetate (1:1).

Procedure—Proceed as directed in the chapter, except to wash the plate in methanol and air-dry it prior to use.

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

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 1: 100 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_{25}H_{30}N_2O_5$ dissolved by employing the procedure set forth in the *Assay*, using a filtered portion of the solution under test as the *Assay preparation*, using methanol to prepare the *Standard preparation*, and making any necessary volumetric adjustments with water.

Tolerances—Not less than 80% (Q) of the labeled amount of $C_{25}H_{30}N_2O_5$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

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PROCEDURE FOR CONTENT UNIFORMITY—

Solvent, *Buffered solvent*, *Mobile phase*, and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Prepare as directed for *Standard preparation* in the *Assay.*

Test solution—Transfer 1 Tablet to a volumetric flask. Add a volume of *Solvent*, equivalent to about one half of the flask volume, sonicate for 5 minutes, and shake by mechanical means for about 15 minutes. Dilute with *Solvent* to volume, mix, and pass through a suitable filter, discarding the first portion of the filtrate. Dilute a portion of the filtrate quantitatively, and stepwise if necessary, with *Solvent* to obtain a solution containing about 0.108 mg of quinapril hydrochloride per mL.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of quinapril ($C_{25}H_{30}N_2O_5$) in each Tablet taken by the formula:

~~$(438.52/474.99)C(L/D)(r_U/r_S)$,~~

$$(438.52/474.98)C(L/D)(r_U/r_S),$$

in which 438.52 and ~~474.99~~ 474.98 are the molecular weights of quinapril and quinapril hydrochloride, respectively; C is the concentration, in mg per mL, of USP Quinapril Hydrochloride RS in the *Standard solution; L* is the labeled quantity, in mg, of quinapril in each Tablet; D is the concentration, in mg per mL, of quinapril hydrochloride in the *Test solution;* and r_U and r_S are the quinapril peak areas obtained from the *Test solution* and the *Standard solution*, respectively.

Related compounds—

Solvent, *Buffered solvent*, and *Mobile phase*—Prepare as directed in the *Assay.*

Resolution solution—Dissolve accurately weighed quantities of USP Quinapril Hydrochloride RS, USP Quinapril Related Compound A RS, and USP Quinapril Related Compound B RS in *Solvent* to obtain a solution having known concentrations of about 0.1 mg of USP Quinapril Hydrochloride RS and 0.005 mg each of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS per mL.

Standard solution—Dissolve accurately weighed quantities of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS in *Solvent*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having known concentrations of about 0.5 µg each of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS per mL.

Test solution—Use the *Assay preparation*.

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *Resolution solution*, and record the peak areas as directed for *Procedure:* the relative retention times are about 0.6 for quinapril related compound B, 1.0 for quinapril, and 2.0 for quinapril related compound A; and the resolution, R, between quinapril and quinapril related compound A and between quinapril and quinapril related compound B is not less than 2.0. Chromatograph the *Standard solution*, and record the peak areas as directed for *Procedure:* the column efficiency is not less than 600 theoretical plates; the tailing factor for the quinapril and quinapril related compound A peaks is less than 1.5 and that for the quinapril related compound B peak is less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for quinapril and not more than 3.0% for each quinapril related compound.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the

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areas for the major peaks. Calculate the quantity, in mg, of each quinapril related compound in the portion of Tablets taken by the formula:

$$500CD(r_U / r_S),$$

in which C is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution; D* is the dilution factor used to prepare the *Test solution;* and r_U and r_S are the peak areas of the corresponding quinapril related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 1.0% of quinapril related compound A is found; not more than 3.0% of quinapril related compound B is found; and not more than 3.6% of total impurities is found.

Assay—

Solvent—Prepare a mixture of water and acetonitrile (65:35).

Buffered solvent—Prepare a mixture of pH 6.5, 0.05 M dibasic potassium phosphate and acetonitrile (65:35).

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and methanesulfonic acid (65:35:0.2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Quinapril Hydrochloride RS in *Solvent* to obtain a solution having a known concentration of about 1.08 mg per mL. Quantitatively dilute with *Buffered solvent* to obtain a solution having a known concentration of about 0.108 mg per mL.

Assay preparation—Transfer 10 Tablets to a 500-mL volumetric flask, add about 300 mL of *Solvent*, and sonicate until the Tablets have disintegrated. Shake by mechanical means for about 15 minutes, dilute with *Solvent* to volume, mix, and centrifuge. Dilute quantitatively, and stepwise if necessary, with *Solvent* to obtain a solution having a concentration of about 0.1 mg of quinapril per mL, and pass through a suitable filter, discarding the first portion of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 6.0-mm × 4-cm column that contains 3-µm packing L10. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation*, and record the peak areas as directed for *Procedure:* the column efficiency is not less than 600 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of quinapril ($C_{25}H_{30}N_2O_5$) in the portion of Tablets taken by the formula:

~~$500CD(438.52/474.99)(r_U / r_S),$~~

$$500CD(438.52/474.98)(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Quinapril Hydrochloride RS in the *Standard preparation; D* is the dilution factor used to prepare the *Assay preparation;* 438.52 and ~~474.99~~ 474.98 are the molecular weights of quinapril and quinapril hydrochloride, respectively; and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

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BRIEFING

Reserpine Tablets, *USP 26* page 1627. It is proposed to reduce the volume of *Dissolution Medium* from 900 mL to 500 mL to increase the sensitivity of the test.

(BPC: M. Marques) RTS—39853-1

Change to read:

Dissolution ⟨711⟩—[NOTE—Do not substitute membrane filters for filter paper where the filtration of reserpine-containing solutions is indicated. Reserpine has been shown to be adsorbed onto membranes.]

Medium: 0.1 N acetic acid; ~~900 mL.~~

■500 mL.■1S (*USP27*)

Apparatus 1: 100 rpm.

Time: 45 minutes.

p-Toluenesulfonic acid solution—Dissolve 1 g of *p*-toluenesulfonic acid in 100 mL of glacial acetic acid.

Standard solution—Dissolve an accurately weighed quantity of USP Reserpine RS in glacial acetic acid, and dilute quantitatively, and stepwise if necessary, with glacial acetic acid to obtain a solution having a known concentration of about 0.1 µg per mL.

Test solution—Pipet an aliquot of the filtered solution under test, containing about 11 µg of reserpine, into a 125-mL separatory funnel. Extract with three 10-mL portions of chloroform, collecting the extracts in a 100-mL volumetric flask, dilute with glacial acetic acid to volume, and mix.

Procedure—Into three individual 50-mL test tubes, pipet 10 mL each of the *Standard solution*, the *Test solution*, and glacial acetic acid to provide the blank. Treat each as follows. Add 10 mL of *p-Toluenesulfonic acid solution*, insert a stopper, and mix gently. Place in a steam bath for 10 minutes. Remove from the steam bath, and cool. Determine the amount of $C_{33}H_{40}N_2O_9$ dissolved from the fluorescences of the *Test solution* and the *Standard solution*, using a suitable spectrophotometer arranged to deliver activation radiation at 390 nm and to measure the resultant fluorescence at the emission wavelength of about 480 nm.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{33}H_{40}N_2O_9$ is dissolved in 45 minutes.

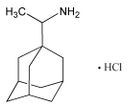
BRIEFING

Rimantadine Hydrochloride, page 5927 of *PF* 24(2) [Mar.–Apr. 1998]. It is proposed to change the solvents used in the tests for *Ordinary impurities*, *Limit of toluene*, and *Assay* to reflect new information.

(PA7b: B. Davani; PSD: C. Okeke) RTS—39422-1

Add the following:

■Rimantadine Hydrochloride



$C_{12}H_{21}N \cdot HCl$ 215.77

Tricyclo[3.3.1.1^{3,7}]-decane-1-methanamine, α-methyl-, hydrochloride.

α-Methyl-1-adamantanemethylamine hydrochloride [*1501-84-4*].

» Rimantadine Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{12}H_{21}N \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store between 15° to 30°.

USP Reference standards ⟨11⟩—*USP Rimantadine Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

X-ray diffraction ⟨941⟩—The X-ray diffraction pattern conforms to that of USP Rimantadine Hydrochloride RS, similarly determined.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩: 20 µg per g.

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Ordinary impurities ⟨466⟩—

Test solution—Transfer 100 mg of Rimantadine Hydrochloride to a 10-mL centrifuge tube, add 2 mL of 1 N sodium hydroxide, and mix. Add 2 mL of ~~methylene chloride,~~ chloroform, and mix on a vortex mixer for 1 minute. Allow the layers to separate, and apply 10 µL of the organic layer.

Standard solution—Proceed as directed for the *Test solution*, using USP Rimantadine Hydrochloride RS in place of the test specimen.

Eluant: a mixture of ethyl acetate, methanol, and ammonium hydroxide (80:10:4).

Procedure—Use a low-actinic glass tank. Dry the plate in a stream of hot air, then heat in an oven at 105° for 30 minutes. Allow the plate to cool to room temperature.

Visualization—Place the plate in an atmosphere of chlorine, prepared by mixing 1.5% potassium permanganate solution and diluted hydrochloric acid (1:1), for about 90 minutes. Allow to air-dry for 60 minutes, and follow with visualization technique 20.

Limit of toluene—

Standard solution—Transfer 10 µL of toluene to a 100-mL volumetric flask, dilute with ~~methylene chloride~~ chloroform to volume, and mix.

Test solution—Transfer about 750 mg of Rimantadine Hydrochloride, accurately weighed, to a 10-mL volumetric flask, dilute with ~~methylene chloride~~ chloroform to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 2-m column that contains 80- to 100-mesh support S1A. The column temperature is maintained at about 200°, and nitrogen is used as the carrier gas. The injection port and detector temperatures are maintained at about 250°. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5 for toluene; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for 9 minutes, and measure the responses for the toluene peaks. Calculate the percentage of toluene in the portion of Rimantadine Hydrochloride taken by the formula:

$$0.867(100/W_U)(r_U/r_S),$$

in which 0.867 is the specific gravity of toluene; W_U is the weight, in mg, of Rimantadine Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the toluene peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.1% is found.

Assay—

Internal standard solution—Transfer about 400 mg of *n*-eicosane to a 250-mL volumetric flask, dilute with ~~methylene chloride~~ hexane to volume, and mix.

Standard preparation—Transfer about 40 mg of USP Rimantadine Hydrochloride RS, accurately weighed, to a 50-mL centrifuge tube, add 15 mL of 1 N sodium hydroxide, and mix. Add 25.0 mL of *Internal standard solution*, and shake by mechanical means for about 15 minutes. Allow the layers to separate, and filter a portion of the ~~lower methylene chloride~~ top hexane layer through anhydrous sodium sulfate. Use the clear filtrate.

Assay preparation—Using about 40 mg of Rimantadine Hydrochloride, accurately weighed, proceed as directed for *Standard preparation.*

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Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 4-mm × 1.8-m glass column that is packed with 3% phase G19 on 100- to 200-mesh support S1A. The column temperature is maintained at about 160°, and the injection port and detector temperatures are maintained at about 250°. Nitrogen is used as the carrier gas. Adjust the carrier flow rate and temperature so that the *n*-eicosane elutes at about 8 minutes. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0 for rimantadine; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{12}H_{21}N \cdot HCl$ in the portion of Rimantadine Hydrochloride taken by the formula:

$$25C(R_U / R_S),$$

in which C is the concentration, in mg per mL, of USP Rimantadine Hydrochloride in the *Standard preparation;* and R_U and R_S are the ratios of the rimantadine peak response to the *n*-eicosane peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

BRIEFING

Rimantadine Hydrochloride Tablets, page 5929 of *PF* 24(2) [Mar.–April 1998]. It is proposed to change the solvents used in the tests for *Identification* and *Assay* to reflect new information.

(PA7b: B. Davani; PSD: C. Okeke) RTS—39422-2

Add the following:

■Rimantadine Hydrochloride Tablets

» Rimantadine Hydrochloride Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{12}H_{21}N \cdot HCl$.

Packaging and storage—Preserve in tight, light-resistant containers, and store between 15° to 30°.

USP Reference standards ⟨11⟩—*USP Rimantadine Hydrochloride RS.*

Identification—

A: The retention time of the rimantadine peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

B: [*Caution—Avoid contact with o-tolidine when performing this test, and conduct the test in a well-ventilated hood.*] Weigh and finely powder not fewer than 5 Tablets. Transfer a portion of the powder, equivalent to 100 mg of rimantadine hydrochloride, to a 10-mL centrifuge tube, add 2 mL of 1 *N* sodium hydroxide, and mix. Add 2 mL of ~~methylene chloride,~~ chloroform and mix on a vortex mixer for 1 minute. Allow the layers to separate, and use the organic layer as the test solution. Separately apply 10 µL

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of the test solution and 10 µL of a Standard solution of USP Rimantadine Hydrochloride RS, similarly prepared, to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel. Place the plate in a low-actinic glass chromatographic chamber, and develop the chromatogram in a solvent system consisting of a mixture of ethyl acetate, methanol, and ammonium hydroxide (80:10:4) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, dry it in a stream of hot air, and then heat in an oven at 105° for 30 minutes. Allow the plate to cool to room temperature. Place the dried plate in an atmosphere of chlorine, prepared from a mixture of 1.5% potassium permanganate solution and 3 N hydrochloric acid (1:1), for about 90 minutes. Remove the plate, and allow it to air-dry for 60 minutes. Prepare a spray reagent as follows. Dissolve 160 mg of *o*-tolidine in 30 mL of glacial acetic acid, dilute with water to 500 mL, add 1 g of potassium iodide, and mix until the potassium iodide is dissolved. Locate the spots on the plate by spraying with the spray reagent: the R_F value of the principal spot in the chromatogram of the test solution corresponds to that of the principal spot obtained from the Standard solution.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Dissolution ⟨711⟩—

Medium: water; 900 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Determine the amount of $C_{12}H_{21}N \cdot HCl$ dissolved, employing the procedure set forth in the *Assay.*

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_{12}H_{21}N \cdot HCl$ is dissolved in 30 minutes.

Assay—

Internal standard solution, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Rimantadine Hydrochloride.*

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg of rimantadine hydrochloride, to a 50-mL centrifuge tube, add 15 mL of 1 N sodium hydroxide, and mix. Add 25.0 mL of *Internal standard solution*, and shake by mechanical means for about 15 minutes. Allow the layers to separate, and filter a portion of the ~~lower methylene chloride~~ top hexane layer through anhydrous sodium sulfate. Use the clear filtrate as the *Assay preparation.*

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{12}H_{21}N \cdot HCl$ in the portion of Tablets taken by the formula:

$$25C(R_U / R_S),$$

in which *C* is the concentration, in mg per mL, of USP Rimantadine Hydrochloride RS in the *Standard preparation;* and R_U and R_S are the ratios of the rimantadine peak response to the *n*-eicosane peak response obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*USP27*)

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BRIEFING

Simethicone, *USP 26* page 1680. In the *Identification* test, it is proposed to specify that toluene should be used as a blank to set the instrument.

(PA4: E. Gonikberg) RTS—39908-1

Change to read:

Identification, *Infrared Absorption* ⟨197S⟩—

■[NOTE—Use toluene as a blank to set the instrument.]■1S (*USP27*)

▲*Test solution*—Prepare as directed for *Assay preparation* in the *Assay.*

Standard solution—Prepare as directed for *Standard preparation* in the *Assay.*▲*USP26*

Cell size: 0.5 mm.

BRIEFING

Monobasic Sodium Phosphate, *USP 26* page 1702. Difficulties have been reported in obtaining reproducible results for *Water* ⟨921⟩ testing of Monobasic Sodium Phosphate monohydrate. The inconsistent results were attributed to the variability in crystal size seen for this material. It is proposed to add a note that monohydrate samples may be ground to a fine powder prior to performing the test.

(PA4: E. Gonikberg) RTS—39389-1

Change to read:

Water, *Method I* ⟨921⟩: less than 2.0% (anhydrous form); between 10.0% and 15.0% (monohydrate); between 18.0% and 26.5% (dihydrate).

■For the monohydrate, the sample may be ground to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results, prior to performing the test.■1S (*USP27*)

BRIEFING

Sorbitol Solution, *USP 26* page 1707 and page 114 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Maltitol Solution*.

(EMC: C. Sheehan) RTS—39694-3

Change to read:

» Sorbitol Solution is an aqueous solution containing ~~;~~ ~~in each 100.0 g,~~

▲▲*USP27*
not less than 64.0 ~~g~~

▲percent▲*USP27*
of D-sorbitol ($C_6H_{14}O_6$). The amounts of total sugars, other polyhydric alcohols, and any hexitol anhydrides, if detected, are not included in the requirements nor

▲in▲*USP27*
the calculated amount under *Other Impurities.*

Change to read:

Packaging and storage— ~~Preserve in tight containers.~~

▲Preserve in well-closed containers. Do not store below 20°.▲*USP27*

Change to read:

Identification—

A: ~~To 3 mL of a 1 in 75 dilution of it in~~

▲Dissolve 1.4 g of Sorbitol Solution in 75 mL of water. Transfer 3 mL of this solution to▲*USP27*
a 15-cm test tube, add 3 mL of freshly prepared catechol solution (1 in 10), mix, add 6 mL of sulfuric acid, mix again, and gently heat the tube in a flame for about 30 seconds: a deep pink or wine color appears.

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

Delete the following:

▲~~**Specific gravity** ⟨841⟩: not less than 1.285.~~▲*USP27*

Delete the following:

▲~~**Refractive index** ⟨831⟩: between 1.455 and 1.465 at 20°.~~▲*USP27*

Add the following:

▲**Microbial limits** ⟨61⟩—The total aerobic microbial count using the *Plate Method* is not more than 10^3 cfu per mL, and the total combined molds and yeasts count is not more than 10^2 cfu per mL.▲*USP27*

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Add the following:

▲**pH** ⟨791⟩: between 5.0 and 7.5, in a 14% (w/w) solution of Sorbitol Solution in carbon dioxide–free water.▲*USP27*

Change to read:

Residue on ignition ⟨281⟩: not more than 0.1%,

▲calculated on the anhydrous basis, determined on a 2-g portion, accurately weighed.▲*USP27*

Delete the following:

▲~~**Chloride** ⟨221⟩—A 2.0-g portion shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid (0.0035%).~~▲*USP27*

Delete the following:

▲~~**Sulfate** ⟨221⟩—A 1.37-g portion shows no more sulfate than corresponds to 0.10 mL of 0.020 N sulfuric acid (0.008%).~~▲*USP27*

Delete the following:

▲~~**Arsenic,** *Method II* ⟨211⟩: 2.5 ppm.~~▲*USP27*

Delete the following:

▲~~**Heavy metals,** *Method I* ⟨231⟩: 0.001%.~~▲*USP27*

Change to read:

Reducing sugars—~~A 10.0-g portion, accurately weighed, meets the requirements of the test for *Reducing sugars* under *Sorbitol*. The amount determined in this test is not included in the calculated amount under *Other Impurities*.~~

■To an amount of Sorbitol Solution, equivalent to 3.3 g on the anhydrous basis, add 3 mL of water, 20.0 mL of cupric citrate TS, and a few glass beads. ~~Proceed as directed in the test for *Reducing sugars* under *Mannitol*, beginning with "Heat so that boiling begins."~~ Heat so that boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS using 2 mL of starch TS, added towards the end of the titration, as an indicator. Not less than 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to not more than 0.3% of reducing sugars, on the anhydrous basis, as glucose. The amount determined in this test is not included in the calculated amount under *Other Impurities*.■1S (*USP27*)

Add the following:

■**Limit of nickel**—

Test solution—Dissolve 20.0 g of Sorbitol Solution in diluted acetic acid, and dilute with diluted acetic acid to 100.0 mL. Add 2.0 mL of a saturated ammonium pyrrolidine dithiocarbamate solution (containing about 10 g of ammonium pyrrolidine dithiocarbamate per liter) and 10.0 mL of methyl isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer.

Blank solution—Prepare as directed for *Test solution*, except to omit the use of the Sorbitol Solution.

Standard solutions—Prepare as directed for *Test solution*, except to prepare three solutions by adding 0.5 mL, 1.0 mL, and 1.5 mL of nickel standard solution TS.

Procedure—~~Proceed as directed in the test for *Nickel* under *Mannitol*.~~ Set the instrument to zero using the *Blank solution*. Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at least three times each, at the wavelength of maximum absorbance at 232.0 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a nickel hollow-cathode lamp and an air–acetylene flame. Record the average of the steady readings for each of the *Standard solutions* and the *Test solution*. Between each measurement, aspirate the *Blank solution*, and ascertain that the reading returns to zero. Plot the absorbances of the *Standard solutions* and the *Test solution* versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the

axes represents the concentration of nickel in the *Test solution*. Not more than 1 µg per g, calculated on the anhydrous basis, is found. ■1S (*USP27*)

Change to read:

Assay—

Mobile phase, *Resolution solution*, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Sorbitol* ~~(see *NF* monograph).~~

Assay preparation— ~~Transfer an accurately weighed portion of Solution, equivalent to about 0.24 g of sorbitol, to a 50-mL volumetric flask, dilute with water to volume, and mix.~~

▲Accurately weigh about 0.12 g of Sorbitol Solution, dissolve in and dilute with water to about 20 g. Accurately record the final solution weight, and mix thoroughly. ▲*USP27*

Procedure—Proceed as directed in the *Assay* under *Sorbitol*. Calculate the ~~quantity, in mg, of $C_6H_{14}O_6$ in the portion of Solution taken by the formula:~~

~~$50C(r_U/r_S)$,~~

~~in which C is the concentration, in mg per mL, of USP Sorbitol RS in the *Standard preparation*;~~

▲percentage of D-sorbitol ($C_6H_{14}O_6$) in the portion of Sorbitol Solution taken by the formula:

$$100(C_S/C_U)(r_U/r_S),$$

in which C_S is the concentration, in mg per g, of USP Sorbitol RS in the *Standard preparation;* C_U is the concentration, in mg per g, of Sorbitol Solution in the *Assay preparation;* ▲*USP27*
and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.

BRIEFING

Spironolactone Tablets, *USP 26* page 1709. On the basis of comments received, it is proposed to revise the *Assay preparation* and the *Procedure* in the *Assay.* The proposed new solvent composition and concentration are consistent with proposed revisions under *Spironolactone* to which *Spironolactone* is cross-referenced [see page 115 of *PF* 29(1)]. Also, in the *Procedure* section of the *Assay* it is proposed to revise the formula for the calculation of the quantity, in mg, of $C_{26}H_{32}O_4S$ in the portion of Tablets taken.

(PA5: A. Wilk) RTS—39864-1

Change to read:

Assay—

Mobile phase, *Standard preparation*, and *Chromatographic system*—Prepare as directed in the *Assay* under *Spironolactone*.

Assay preparation—Accurately weigh 20 Tablets, and transfer to a 1000-mL volumetric flask, add 100 mL of water, and sonicate for 15 minutes or until the Tablets are disintegrated, and then cool for 10 minutes. Add ~~700 mL~~

■500 mL■1S (*USP27*)
of acetonitrile, shake for 30 minutes, and then sonicate for an additional 30 minutes. Cool to room temperature, dilute with ~~acetonitrile~~

■water■1S (*USP27*)
to volume, and mix. Centrifuge a portion of the mixture at about 3000 rpm for 10 minutes. Dilute an accurately measured portion of the supernatant, expected to contain 25 mg of spironolactone, quantitatively, and stepwise if necessary, with a mixture of acetonitrile and water ~~(9:1)~~

■(1:1)■1S (*USP27*)
to obtain a solution having a concentration of ~~0.25 mg~~

■0.5 mg■1S (*USP27*)
of spironolactone per mL.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Spironolactone.* Calculate the quantity, in mg, of $C_{24}H_{32}O_4S$ in the portion of Tablets taken by the formula:

~~$0.1C(r_U/r_S)$,~~

■$50C(r_U/r_S)$,■1S (*USP27*)

in which C is the concentration, in ~~µg~~

■mg■1S (*USP27*)
per mL, of USP Spironolactone RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained for spironolactone from the *Assay preparation* and the *Standard preparation*, respectively.

BRIEFING

Trimethoprim, *USP 26* page 1893. In *Identification* test *B*, the calculation for the respective UV absorptivities has been clarified to reflect the new approved labeling requirement for USP Trimethoprim RS, changing the directions for use. (See *USP Reference Standards* ⟨11⟩, appearing elsewhere in this number of *PF*).

(PA7b: B. Davani) RTS—39909-1

In-Process Revision

Change to read:

Identification—

A: *Infrared Absorption* ⟨197S⟩—
Solution: 1 in 100.
Medium: chloroform.

B: Transfer about 100 mg of it, accurately weighed, to a 100-mL volumetric flask, and dissolve in 25 mL of alcohol. Dilute quantitatively and stepwise with sodium hydroxide solution (1 in 250) to obtain a 1 in 50,000 solution: the UV absorption spectrum of this solution exhibits maxima and minima only at the same wavelengths as that of a similar solution of USP Trimethoprim RS, concomitantly measured; and the respective absorptivities, calculated on the dried basis

■for the test sample only,■1S (*USP27*) at the wavelength of maximum absorbance at about 287 nm do not differ by more than 3.0%.

BRIEFING

Valsartan and Hydrochlorothiazide Tablets, page 129 of *PF* 29(1) [Jan.–Feb. 2003]. As recommended by the USP Reference Standards Committee, it is proposed to change the name of the impurity 4-amino-6-chloro-1,3-benzenedisulfonamide to benzothiadiazine related compound A for the official USP Reference Standard.

(PA5: A. Wilk) RTS—39855-1

Add the following:

■Valsartan and Hydrochlorothiazide Tablets

» Valsartan and Hydrochlorothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—~~*USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS.*~~ *USP Benzothiadiazine Related Compound A RS. USP Hydrochlorothiazide RS. USP Valsartan RS. USP Valsartan Related Compound B RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—To a centrifuge tube transfer an amount of ground Tablets, equivalent in weight to a single Tablet, add 2.0 mL of acetone, sonicate for 15 minutes, and centrifuge.

Application volume: 2 µL.

Developing solvent system: a mixture of ethyl acetate, dehydrated alcohol, and a solution (25 in 100) of ammonium hydroxide (8:2:1).

Procedure—Proceed as directed in the chapter, except to develop the plate in a paper-lined chromatographic chamber equilibrated with *Developing solvent system* for about 15 minutes prior to use. Allow the chromatogram to develop until the solvent front has moved at least 7 cm. After removing the plate and marking the solvent front, dry the plate under a current of warm air until it is completely dry. The R_F values of the principal spots obtained from the *Test solution* correspond to those obtained from the Standard solution.

B: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 50 rpm.

Time: ~~45~~ 30 minutes.

Procedure—Determine the amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved by employing UV absorption at the wavelengths of maximum absorbance at about 250 nm for valsartan ~~(cor-~~

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~~rected for interference from hydrochlorothiazide on the basis of the absorbances of hydrochlorothiazide at 250 and 272 nm)~~ and at about 272 nm for hydrochlorothiazide on filtered portions of the solution under test, ~~suitably diluted with *Dissolution Medium*, in comparison with a Standard solution having known concentrations of USP Valsartan RS and USP Hydrochlorothiazide RS in the same *Medium*~~ diluted with *Medium* if necessary. Calculate the quantity of $C_{24}H_{29}N_5O_3$ dissolved, in mg, by the formula:

$$1000D\left(\frac{A_{\text{obs250}}a_{\text{H272}} - A_{\text{obs272}}a_{\text{H250}}}{a_{\text{V250}}a_{\text{H272}} - a_{\text{V272}}a_{\text{H250}}}\right),$$

in which D is the sample dilution factor if used; A_{obs250} is the observed absorbance of the sample solution at 250 nm; A_{obs272} is the observed absorbance of the sample solution at 272 nm; a_{V250} is the absorptivity of valsartan at 250 nm; a_{V272} is the absorptivity of valsartan at 272 nm; a_{H250} is the absorptivity of hydrochlorothiazide at 250 nm; and a_{H272} is the absorptivity of hydrochlorothiazide at 272 nm. The absorptivities, a, are determined from separate Standard solutions of USP Valsartan RS and USP Hydrochlorothiazide RS in the *Medium* having known concentration and expressed in units as defined by *Spectrophotometry and Light-Scattering* ⟨851⟩. Calculate the quantity of $C_7H_8ClN_3O_4S_2$ dissolved, in mg, by the formula:

$$1000D\left(\frac{A_{\text{obs272}}a_{\text{V250}} - A_{\text{obs250}}a_{\text{V272}}}{a_{\text{V250}}a_{\text{H272}} - a_{\text{V272}}a_{\text{H250}}}\right),$$

in which the terms are as defined above.

Tolerances—Not less than ~~75%~~ 80% (Q) of the labeled amounts of $C_{24}H_{29}N_5O_3$ and $C_7H_8ClN_3O_4S_2$ is dissolved in ~~45~~ 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Diluent, *Solution A*, *Solution B*, *Mobile phase*, and *Chromatographic system*—Prepare as directed in the *Assay.*

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

Test solution—Place 1 Tablet in a 200-mL volumetric flask, add 5 mL of water, and allow to stand for 5 minutes. Add about 100 mL of *Diluent*, and sonicate for 15 minutes. Dilute with *Diluent* to volume, mix, and centrifuge a portion of this solution at about 3000 rpm. Quantitatively dilute a volume of the clear supernatant with *Diluent* to obtain a solution having a concentration of about 0.2 mg of valsartan per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the quantities, in mg, of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the Tablet taken by the formula:

$$(LC_S/C_U)(r_U/r_S),$$

in which L is the labeled quantity, in mg, of the relevant analyte in the Tablet; C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution;* C_U is the concentration, in mg per mL, of the corresponding analyte in the *Test solution*, based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution*, respectively.

Related compounds—

Diluent, *Solution A*, *Solution B*, and *Mobile phase*—Prepare as directed in the *Assay.*

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Standard stock solution—Dissolve accurately weighed quantities of ~~USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS,~~ USP Benzothiadiazine Related Compound A RS, USP Hydrochlorothiazide RS, USP Valsartan RS, and USP Valsartan Related Compound B RS in *Diluent* to obtain a solution having known concentrations of about 0.03 mg per mL, 0.06 mg per mL, 0.08 mg per mL, and 0.2 mg per mL, respectively.

Resolution solution—Dilute 5.0 mL of *Standard stock solution* with *Diluent* to 100.0 mL, and mix.

Standard solution—Dilute 10.0 mL of *Resolution solution* with *Diluent* to 100.0 mL, and mix.

Test solution—Use the *Assay preparation* as specified.

Chromatographic system—Prepare as directed in the *Assay*. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between valsartan related compound B and valsartan, and between ~~4-amino-6-chloro-1,3-benzenedisulfonamide~~ benzothiadiazine related compound A and hydrochlorothiazide is not less than 1.4. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation, determined from the valsartan and hydrochlorothiazide peaks, for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks, disregarding the peak, if any, with a retention time of about 22 minutes. Calculate the quantity, in mg, of each impurity in the portion of Tablets taken by the formula:

$$2000C(r_U / r_S),$$

in which *C* is the concentration, in mg per mL, of ~~USP Valsartan Related Compound B RS or USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS,~~ USP Benzothiadiazine Related Compound A RS, or the relevant USP Reference Standard (when determining the quantity of other impurities) in the *Standard solution;* and r_U and r_S are the corresponding peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than ~~0.5%~~ 1.0% ~~each of valsartan related compound B and~~ of ~~4-amino-6-chloro-1,3-benzenedisulfonamide~~ benzothiadiazine related compound A is found; not more than 0.2% of any other impurity, excluding valsartan related compound A and valsartan related compound B, is found; and not more than ~~0.8%~~ 1.3% of total impurities, excluding valsartan related compound A and valsartan related compound B, is found. [NOTE—Valsartan related compound A is the enantiomer of valsartan and coelutes with valsartan in this test.]

Assay—

Diluent—Prepare a mixture of acetonitrile and water (1:1).

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (90:10:0.1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, water, and trifluoroacetic acid (90:10:0.1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 12.5 mg of USP Hydrochlorothiazide RS, accurately weighed, to a 200-mL volumetric flask. Add about 12.5*J* mg of USP Valsartan RS, accurately weighed, *J* being the ratio of the labeled amount, in mg, of valsartan to the labeled amount, in mg, of hydrochlorothiazide per Tablet. Add about 100 mL of *Diluent*, sonicate for 15 minutes, dilute with *Diluent* to volume, and mix. Transfer 25.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Quan-

titatively dilute a volume of this solution with *Diluent* to obtain a solution having a known concentration of about 0.2 mg of USP Valsartan RS per mL.

Assay preparation—Transfer a number of Tablets, equivalent to about 62.5 mg of hydrochlorothiazide, to a 250-mL volumetric flask. Add 5 mL of water, and allow to stand for 5 minutes. Then add about 100 mL of *Diluent*, sonicate for 15 minutes, and shake for 30 minutes. Dilute with *Diluent* to volume, mix, and centrifuge a portion of this solution at 3000 rpm. Dilute 25.0 mL of the clear supernatant with *Diluent* to 200.0 mL, and mix (*Solution 1*). [NOTE—Retain a portion of *Solution 1* to use as the *Test solution* in the test for *Related compounds*.] Dilute an accurately measured volume of *Solution 1* with *Diluent* to obtain a solution containing about 0.2 mg of valsartan per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 265-nm detector and a 3.0-mm × 12.5-cm column that contains 5-µm packing L1. The flow rate is about 0.4 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–25	90→10	10→90	linear gradient
25–27	10→90	90→10	linear gradient
27–40	90	10	isocratic

Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the quantities, in mg, of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken by the formula:

$$(LC_S/C_U)(r_U/r_S),$$

in which L is the labeled quantity, in mg, of the relevant analyte in each Tablet; C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard preparation;* C_U is the concentration, in mg per mL, of the corresponding analyte in the *Assay preparation*, based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■1S (*USP27*)

BRIEFING

Bacteriostatic Water for Injection, *USP 26* page 1939; **Sterile Water for Inhalation,** *USP 26* page 1939; **Sterile Water for Injection,** *USP 26* page 1939; **Sterile Water for Irrigation,** *USP 26* page 1939; **Sterile Purified Water** *USP 26* page 1940 and page 1272 of *PF* 28(4) [July–Aug. 2002]. In accordance with numerous requests received, the Expert Committee on Pharmaceutical Waters proposes to replace the various cross-references in all of the water monographs with a listing of the actual test requirements for each monograph. Although cross-referencing is established USP publication policy, it is recommended that the policy be waived in recognition of the fact that many readers in the field of water treatment are not regular users of *USP* and are not familiar with the cross-referencing style. It was also recommended that the *Note* under *Purified Water*, recently added to direct the reader to general information chapter ⟨1231⟩, also be added to all of the water monographs. It is proposed to add this *Note* for informational purposes only, and, therefore, to place it above and outside of the Definition.

It should be noted that the revision of all packaged water monographs is presently under study. However, because this action will take time, the revisions proposed herein are suggested as an interim measure to improve readability of the monographs. New proposals based on studies of the scientific content of the monographs will likely be published in *PF* early next year.

(PW: F. Barletta) RTS—39787-2

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Add the following:

■NOTE—For microbiological guidance see general information chapter *Water for Pharmaceutical Purposes* ⟨1231⟩.■1S (*USP27*)

Add the following:

■**Sterility** ⟨71⟩: meets the requirements.■1S (*USP27*)

Add the following:

■**Particulate matter** ⟨788⟩: meets the requirements.■1S (*USP27*)

Add the following:

■**Calcium**—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.■1S (*USP27*)

Add the following:

■**Carbon dioxide**—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.■1S (*USP27*)

Add the following:

■**Sulfate**—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.■1S (*USP27*)

Delete the following:

■~~**Other requirements**—It meets the requirements of the test for *Particulate matter* under *Sterile Water for Injection* and all of the tests under *Sterile Purified Water*, except the tests for *pH*, *Ammonia*, *Chloride*, and *Oxidizable substances*.~~■1S (*USP27*)

BRIEFING

Sterile Water for Inhalation, *USP 26* page 1939—See briefing under *Bacteriostatic Water for Injection*.

(PW: F. Barletta) RTS—39787-1

Add the following:

■NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* ⟨1231⟩.■1S (*USP27*)

Add the following:

■**Sterility** ⟨71⟩: meets the requirements.■1S (*USP27*)

Add the following:

■**Ammonia**—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia (furnished by using 1.76 mL of 1.0 N ammonium hydroxide) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per liter for containers having a fill volume of less than 50 mL and 0.3 mg per liter where the fill volume is 50 mL or more.■1S (*USP27*)

Add the following:

■**Calcium**—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.■1S (*USP27*)

Add the following:

■**Carbon dioxide**—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.■1S (*USP27*)

Add the following:

■**Chloride**—To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩) containing 10 µg of chloride (0.5 mg per liter), viewed downward over a dark surface with light entering the tubes from the sides.■1S (*USP27*)

Add the following:

■**Sulfate**—To 100 mL add l mL of barium chloride TS: no turbidity is produced.■1S (*USP27*)

Add the following:

■**Oxidizable substances**—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Inhalation in containers having a fill volume of less than 50 mL, add 0.4 mL of 0.1 N potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of 0.1 N potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and filter through a sintered-glass filter: the pink color does not completely disappear.■1S (*USP27*)

Delete the following:

■~~**Other requirements**—It meets the requirements of all the tests under *Sterile Purified Water* except the test for *pH*.~~■1S (*USP27*)

BRIEFING

Sterile Water for Injection, *USP 26* page 1939—See briefing under *Bacteriostatic Water for Injection*.

(PW: F. Barletta) RTS—39787-5

Add the following:

■NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* ⟨1231⟩.■1S (*USP27*)

Add the following:

■**Sterility** ⟨71⟩: meets the requirements.■1S (*USP27*)

Add the following:

■**pH** ⟨791⟩: between 5.0 and 7.0 in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.■1S (*USP27*)

Add the following:

■**Ammonia**—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia (furnished by using 1.76 mL of 1.0 N ammonium hydroxide) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per liter for containers having a fill volume of less than 50 mL and 0.3 mg per liter where the fill volume is 50 mL or more.■1S (*USP27*)

Add the following:

■**Calcium**—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.■1S (*USP27*)

Add the following:

■**Carbon dioxide**—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.■1S (*USP27*)

Add the following:

■**Chloride**—To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩) containing 10 µg of chloride (0.5 mg per liter), viewed downward over a dark surface with light entering the tubes from the sides.■1S (*USP27*)

Add the following:

■**Sulfate**—To 100 mL add 1 mL of barium chloride TS: no turbidity is produced.■1S (*USP27*)

Add the following:

■**Oxidizable substances**—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Injection in containers having a fill volume of less than 50 mL, add 0.4 mL of 0.1 N potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of 0.1 N potassium permanganate, and boil for 5 min-

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utes. If a precipitate forms, cool in an ice bath to room temperature, and filter through a sintered-glass filter: the pink color does not completely disappear.■1S (*USP27*)

Delete the following:

■~~**Other requirements**—It meets the requirements of all the tests under *Sterile Purified Water*.~~■1S (*USP27*)

BRIEFING

Sterile Water for Irrigation, *USP 26* page 1939—See briefing under *Bacteriostatic Water for Injection*.

(PW: F. Barletta) RTS—39787-3

Add the following:

■NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* ⟨1231⟩.■1S (*USP27*)

Add the following:

■**Bacterial endotoxins** ⟨85⟩: not more than 0.25 Endotoxin Unit per mL.■1S (*USP27*)

Add the following:

■**Sterility** ⟨71⟩: meets the requirements.■1S (*USP27*)

Add the following:

■**pH** ⟨791⟩: between 5.0 and 7.0 in a solution containing 0.3 mL of saturated potassium chloride solution per 100 mL of test specimen.■1S (*USP27*)

Add the following:

■**Ammonia**—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia (furnished by using 1.76 mL of 1.0 N ammonium hydroxide) in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per liter for containers having a fill volume of less than 50 mL and 0.3 mg per liter where the fill volume is 50 mL or more.■1S (*USP27*)

Add the following:

■**Calcium**—To 100 mL add 2 mL of ammonium oxalate TS: no turbidity is produced.■1S (*USP27*)

Add the following:

■**Carbon dioxide**—To 25 mL add 25 mL of calcium hydroxide TS: the mixture remains clear.■1S (*USP27*)

Add the following:

■**Chloride**—To 20 mL in a color-comparison tube add 5 drops of nitric acid and 1 mL of silver nitrate TS, and gently mix: any turbidity formed within 10 minutes is not greater than that produced in a similarly treated control consisting of 20 mL of *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩) containing 10 µg of chloride (0.5 mg per liter), viewed downward over a dark surface with light entering the tubes from the sides.■1S (*USP27*)

Add the following:

■**Sulfate**—To 100 mL add l mL of barium chloride TS: no turbidity is produced.■1S (*USP27*)

Add the following:

■**Oxidizable substances**—To 100 mL add 10 mL of 2 N sulfuric acid, and heat to boiling. For Sterile Water for Irrigation in containers having a fill volume of less than 50 mL, add 0.4 mL of 0.1 N potassium permanganate, and boil for 5 minutes; where the fill volume is 50 mL or more, add 0.2 mL of 0.1 N potassium permanganate, and boil for 5 minutes. If a precipitate forms, cool in an ice bath to room temperature, and filter through a sintered-glass filter: the pink color does not completely disappear.■1S (*USP27*)

Delete the following:

■~~**Other requirements**—It meets the requirements of all of the tests under *Sterile Purified Water* and the *Bacterial endotoxins* test under *Water for Injection*.~~■1S (*USP27*)

BRIEFING

Sterile Purified Water, *USP 26* page 1940 and page 1272 of *PF* 28(4) [July–Aug. 2002]—See briefing under *Bacteriostatic Water for Injection*.

(PW: F. Barletta) RTS—39787-4

Add the following:

■NOTE—For microbiological guidance, see general information chapter *Water for Pharmaceutical Purposes* ⟨1231⟩.■1S (*USP27*)

Change to read:

Ammonia—For containers having a fill volume of less than 50 mL, dilute 50 mL of it with 50 mL of *High-Purity Water* (see *Reagents* under *Containers* ⟨661⟩), and use this dilution as the test solution; where the fill volume is 50 mL or more, use 100 mL of it as the test solution. To 100 mL of the test solution add 2 mL of alkaline mercuric-potassium iodide TS: any yellow color produced immediately is not darker than that of a control containing 30 µg of added ammonia

■(furnished by adding 1.76 mL of 1.0 N ammonium hydroxide)■1S (*USP27*)

in 100 mL of *High-Purity Water*. This corresponds to a limit of 0.6 mg per liter for containers having a fill volume of less than 50 mL and 0.3 mg per liter where the fill volume is 50 mL or more.

BRIEFING

Excipients, USP and NF Excipients, Listed by Categories, *NF 21* page 2679 and page 684 of *PF* 29(3) [May–June 2003]. The proposed revisions complement the proposed new monographs *Polyoxyl Lauryl Ether*, *Polyoxyl Stearyl Ether*, *Sodium Cetostearyl Sulfate*, and *Stearoyl Polyoxylglycerides*, which appear elsewhere in this number of *PF*.

(EMC; NL) RTS—39918; 39918-5; 39930-1; 39843-1

Change to read:

Antimicrobial Preservative

Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben

▲Cetrimonium Bromide▲*NF22*
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol

▲2-Phenoxyethanol▲*NF22*
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

Change to read:

Coating Agent

Carboxymethylcellulose Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate

▲Cellulose Acetate Butyrate▲*NF22*
Cellulose Acetate Phthalate (see Cellacefate)

▲Copovidone▲*NF22*

▲Corn Syrup Solids▲*NF22*
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
~~Hydroxypropyl Methylcellulose~~
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)

▲Hypromellose▲*NF22*

▲Hypromellose Acetate Succinate▲*NF22*
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion

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Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac

▲Starch, Pregelatinized Modified▲*NF22*
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:
Emollient
Alkyl (C12-15) Benzoate

■Hydrogenated Soybean Oil■1S (*NF22*)

Change to read:
Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)

■Diethylene Glycol ~~Monostearates~~ Stearates■1S (*NF22*)

■Ethylene Glycol ~~Monostearates~~ Stearates■1S (*NF22*)

▲Glyceryl Distearate▲*NF22*

▲Glyceryl Monolinoleate▲*NF22*

▲Glyceryl Monooleate▲*NF22*
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil
■Polyoxyl Lauryl Ether■1S (*NF22*)
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate

■Polyoxyl Stearyl Ether■1S (*NF22*)
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate

■Sodium Cetostearyl Sulfate■1S (*NF22*)
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:
Humectant

▲Corn Syrup Solids▲*NF22*
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol

▲Sorbitol, Anhydrized Liquid▲*NF22*

Change to read:
Ointment Base

~~Caprylocaproyl Macrogolglycerides~~

■Caprylocaproyl Polyoxylglycerides■1S (*NF22*)
Diethylene Glycol Monoethyl Ether

▲Lauroyl Macrogolglycerides▲*NF22*

~~Lineoyl Macrogolglycerides~~

■Lineoyl Polyoxylglycerides■1S (*NF22*)
Lanolin
Ointment, Hydrophilic
Ointment, White

~~Oleoyl Macrogolglycerides~~

■Oleoyl Polyoxylglycerides■1S (*NF22*)
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water Ointment
Squalane

~~Stearoyl Macrogolglycerides~~

■Stearoyl Polyoxylycerides■1S (*NF22*)
Vegetable Oil, Hydrogenated, Type II

Change to read:
Plasticizer
Acetyltributyl Citrate

Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
Propylene Glycol

▲Sorbitol, Anhydrized Liquid▲*NF22*
Triacetin
Tributyl Citrate
Triethyl Citrate

Change to read:
Polymer Membrane
Cellulose Acetate

▲Cellulose Acetate Butyrate▲*NF22*

Change to read:
Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol

~~Caprylocaproyl Macrogolglycerides~~

■Caprylocaproyl Polyoxylglycerides■1S (*NF22*)
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol

▲Lauroyl Macrogolglycerides▲*NF22*

~~Lineoyl Macrogolglycerides~~

▲Lineoyl Polyoxylglycerides▲*NF22*
Methyl Alcohol
Methyl Isobutyl Ketone
Mineral Oil

~~Oleoyl Macrogolglycerides~~

■Oleoyl Polyoxylglycerides■1S (*NF22*)
Peanut Oil
Polyethylene Glycol
Propylene Glycol
Sesame Oil

~~Stearoyl Macrogolglycerides~~

■Stearoyl Polyoxylglycerides■1S (*NF22*)
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:
Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

▲Corn Syrup Solids▲*NF22*
Dextrin
Gelatin

▲Gellan Gum▲*NF22*
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose

~~Hydroxypropyl Methylcellulose~~

▲Hypromellose▲*NF22*
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate

▲Tapioca Starch▲*NF22*
Tragacanth
Xanthan Gum

Change to read:
Sweetening Agent
Aspartame

▲Aspartame Acesulfame▲*NF22*

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▲Corn Syrup Solids▲*NF22*
Dextrates
Dextrose
Dextrose Excipient
Fructose

▲Maltose▲*NF22*
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

Change to read:
Tablet Binder
Acacia
Alginic Acid
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline

▲Copovidone▲*NF22*

▲Corn Syrup Solids▲*NF22*
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum

▲Hypromellose▲*NF22*

▲Hypromellose Acetate Succinate▲*NF22*
~~Hydroxypropyl Methylcellulose~~

▲Maltose▲*NF22*
Methylcellulose
Polyethylene Oxide
Povidone
Starch, Pregelatinized
▲Starch, Pregelatinized Modified▲*NF22*
Syrup

▲Tapioca Starch▲*NF22*

Change to read:
Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic
Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered

▲Corn Syrup Solids▲*NF22*
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose

▲Maltose▲*NF22*
Mannitol
Sorbitol
Starch
Starch, Pregelatinized

▲Starch, Pregelatinized Modified▲*NF22*
Sucrose
Sugar, Compressible
Sugar, Confectioners

▲Tapioca Starch▲*NF22*

Change to read:
Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

▲Maltose▲*NF22*
Polacrilin Potassium
Sodium Starch Glycolate
Starch
Starch, Pregelatinized

▲Starch, Pregelatinized Modified▲*NF22*

▲Tapioca Starch▲*NF22*

Change to read:
Tonicity Agent

▲Corn Syrup Solids▲*NF22*
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:
Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

▲Corn Syrup Solids▲*NF22*
Peppermint Water
Sorbitol Solution
Syrup

OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

MONOGRAPHS (NF)

BRIEFING

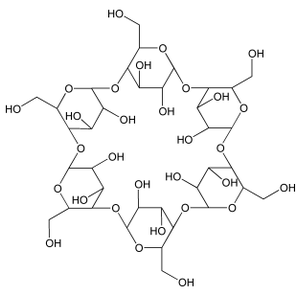
Alfadex, page 1611 of *PF* 28(5) [Sept.–Oct. 2002]. This new monograph, which previously appeared in *Pharmacopeial Previews*, is now being forwarded with editorial style changes to *In-Process Revision*. It is also proposed to add storage conditions to the *Packaging and storage* section. The molecular weight of Alfadex is revised to reflect the current atomic weight values published in *USP 26*.

(EMC: E. Gonikberg; PSD: C. Okeke) RTS—39918-3

In-Process Revision

Add the following:

■Alfadex



$(C_6H_{10}O_5)_6$ ~~972.85~~ 972.84

Alpha cyclodextrin [*10016-20-3*].

» Alfadex is composed of six alpha-(1-4) linked D-glucopyranosyl units. It contains not less than 98.0 percent and not more than 101.0 percent of $(C_6H_{10}O_5)_6$, calculated on the dried basis.

Packaging and storage—Preserve in tight containers. Store at up to 25°, excursion permitted between 15° and 30°. Avoid excessive heat and freezing. Protect from moisture.

USP Reference standards ⟨11⟩—*USP Alpha Cyclodextrin RS. USP Beta Cyclodextrin RS. USP Gamma Cyclodextrin RS.*

Clarity of solution—Dissolve 1.0 g in 100.0 mL of previously boiled and cooled water: the resulting solution is clear.

Identification—

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

B: It meets the requirements of the test for *Specific rotation* ⟨781S⟩.

C: Mix 0.2 g with 2 mL of iodine TS, warm in a water bath to dissolve the test specimen, and allow to stand at room temperature: a yellow-brown precipitate is formed.

Specific rotation ⟨781S⟩: between +147° and +152° (t = 20°).

Test solution: 10 mg per mL, in water.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*. The total aerobic bacterial count does not exceed 1000 per g.

pH ⟨791⟩—The pH of the mixture of 30 mL of its aqueous solution (1 in 100) and 1 mL of *Potassium chloride solution* is 5.0 to 8.0.

Potassium chloride solution—Transfer 22.4 g of potassium chloride into a 100-mL volumetric flask, and dilute with water to volume.

Loss on drying ⟨731⟩—Dry 1.0 g of it at 120° for 2 hours: it loses not more than 10.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%, determined on 1.0 g.

Heavy metals, *Method II* ⟨231⟩: 10 µg per g.

Reducing sugars—

Cupric solution—Dissolve 15 g of cupric sulfate in water to make 100 mL.

Tartrate solution—Dissolve 2.5 g of anhydrous sodium carbonate, 2.5 g of potassium sodium tartrate, 2.0 g of sodium bicarbonate, and 20 g of anhydrous sodium sulfate in water to make 100 mL.

Cupric–tartaric solution—Immediately before use, mix 1 part of *Cupric solution* with 25 parts of *Tartrate solution*.

Ammonium molybdate reagent—Mix 10 mL of a solution of disodium arsenate (6 in 100), 50 mL of a solution of ammonium molybdate (1 in 10), and 90 mL of diluted sulfuric acid, and dilute with water to 200 mL.

Test solution—Transfer about 1.0 g of Alfadex, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water that has been previously boiled and cooled to room temperature, to volume, and mix. To 1 mL of this solution add 1 mL of *Cupric–tartaric solution*. Heat on a water bath for 10 minutes, then cool to room temperature. Add 10 mL of *Ammonium molybdate reagent*, and allow to stand for 15 minutes.

Standard solution—Prepare at the same time and in the same manner as the *Test solution*, using 1 mL of a glucose solution that contains 20 mg in 1 liter.

Procedure—Concomitantly measure the absorbance of the *Test solution* and the *Standard solution* at the wavelength of maximum absorbance at 740 nm relative to that of water, with a suitable spectrophotometer. The absorbance of the *Test solution* is not greater than that of the *Standard solution* (0.2%).

Related compounds—

System suitability solution—Prepare as directed for *System suitability preparation* in the *Assay.*

Standard solution—Transfer 5.0 mL of the *System suitability solution* into a 50-mL volumetric flask, and dilute with water to volume.

Test solution—Use the *Assay stock preparation* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. For the *Test solution*, the areas of any peaks corresponding to beta cyclodextrin or to gamma cyclodextrin are not greater than half of the area of the corresponding peaks in the chromatogram of the *Standard solution* (0.25%), and the sum of the areas of all the

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peaks, excluding the principal peak and the peaks corresponding to beta cyclodextrin or to gamma cyclodextrin, is not greater than half of the area of the peak corresponding to alpha cyclodextrin in the chromatogram of the *Standard solution* (0.5%).

Light-absorbing impurities—

Test solution—Transfer about 1.0 g of Alfadex, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water, which has been previously boiled and cooled to room temperature, to volume, and mix.

Procedure—Determine the absorbance of the *Test solution* in a 1-cm cell with a suitable spectrophotometer, after correcting for the blank: between 230 nm and 350 nm, the absorbance is not greater than 0.10; and between 350 nm and 750 nm, the absorbance is not greater than 0.05.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (90:10, v/v). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer 25 mg of USP Alpha Cyclodextrin RS, accurately weighed, in 25-mL volumetric flask, and dissolve in and dilute with water to volume.

System suitability preparation—Transfer 25 mg of USP Beta Cyclodextrin RS, 25 mg of USP Gamma Cyclodextrin RS, and 50 mg of USP Alpha Cyclodextrin RS, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water, and mix.

Assay stock preparation—Dissolve 250 mg of Alfadex, accurately weighed, in water with the aid of heat. Cool, and dilute to 25.0 mL with water to volume.

Assay preparation—Transfer 5.0 mL of the *Assay stock preparation* to a 50-mL volumetric flask, and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 4.6-mm × 25-cm column that contains 10-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability preparation*, and record the chromatograms for about 3.5 times the retention time of alpha cyclodextrin. Record the peak responses as directed for *Procedure:* the retention time of alpha cyclodextrin is about 4.5 minutes; the relative retention times are about 1.0 for alpha cyclodextrin, about 2.2 for beta cyclodextrin, and about 0.7 for gamma cyclodextrin; the resolution, R, between the gamma cyclodextrin and alpha cyclodextrin peaks is not less than 1.5; and for the alpha cyclodextrin peak, the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $(C_6H_{10}O_5)_6$ in the portion of Alfadex taken by the formula:

$$2500(C/W)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of alpha cyclodextrin in the *Standard preparation*, calculated on the dried basis, as determined from the concentration of USP Alpha Cyclodextrin RS corrected for the declared moisture content; W is the weight, in mg, of alpha cyclodextrin taken to prepare the *Assay stock preparation;* and R_U and R_S are the peak responses of the alpha cyclodextrin peak obtained from the *Assay preparation* and the *Standard preparation*, respectively.■1S (*NF22*)

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BRIEFING

Low-Substituted Carboxymethylcellulose Sodium, page 1617 of *PF* 28(5) [Sept.–Oct. 2002]. This new monograph, which previously appeared in *Pharmacopeial Previews*, is now forwarded to *In-Process Revision*. It is proposed to add storage conditions to the *Packaging and storage* section.

(EMC: E. Gonikberg; PSD: C. Okeke) RTS—39918-2

Add the following:

■Low-Substituted Carboxymethylcellulose Sodium

Cellulose, carboxymethyl ether, sodium salt, low-substituted.

Carmellose sodium, low-substituted [*9004-32-4*].

» Low-Substituted Carboxymethylcellulose Sodium is the sodium salt of a partly *O*-(carboxymethylated) cellulose. It contains not less than 2.0 percent and not more than 4.5 percent of sodium (Na), calculated on the dried basis.

Packaging and storage—Preserve in ~~a~~ tight containers. Store at up to 25°, excursions permitted between 15° and 30°. Avoid excessive heat and freezing. Protect from moisture.

Labeling—When the settling volume is determined, label it to indicate the settling volume value.

Identification—

A: Shake 1 g of Low-Substituted Carboxymethylcellulose Sodium with 100 mL of sodium hydroxide solution (1 in 10): a suspension is produced.

B: Shake 1 g of Low-Substituted Carboxymethylcellulose Sodium with 50 mL of water. Transfer 1 mL of the mixture to a test tube, and add 1 mL of water and 1 mL of 1-naphthol TS. Incline the test tube, and add carefully 2 mL of sulfuric acid down the side so that it forms a lower layer: a reddish-purple color develops at the interface.

C: It meets the requirements of the test for *Residue on ignition.*

D: The solution prepared in the test for *Heavy metals* responds to the pyroantimonate precipitate test for *Sodium* ⟨191⟩.

pH ⟨791⟩—Shake 1 g of Low-Substituted Carboxymethylcellulose Sodium with 100 mL of carbon dioxide–free water, and centrifuge: the pH of the suspension is between 6.0 and 8.5.

Loss on drying ⟨731⟩—Dry 1.0 g of Low-Substituted Carboxymethylcellulose Sodium at 105° for 3 hours: it loses not more than 10.0% of its weight.

Settling volume—[NOTE—The following test, which can relate to excipient function, may be carried out, depending on the intended use in the formulation. In cases where there are no concerns regarding the settling volume of this article, this test may be omitted.] Where the labeling states the settling volume, determine the settling volume as follows. In a 100-mL graduated cylinder, transfer 20 mL of isopropyl alcohol, add 5.0 g of Low-Substituted Carboxymethylcellulose Sodium, and shake vigorously. Dilute with isopropyl alcohol to 30 mL, then with water to 50 mL, and shake vigorously. Within 15 minutes, repeat the shaking three times. Allow to stand for 4 hours, and determine the volume of the settled mass: it is between 15.0 mL and 35.0 mL.

Residue on ignition ⟨281⟩—Determined on 1.0 g of Low-Substituted Carboxymethylcellulose Sodium using a mixture of sulfuric acid and water (1:1) and an ignition temperature of 600 ± 50°: it is between 6.5% and 13.5%, calculated on the dried basis.

Water-soluble substances—Disperse 5.0 g of Low-Substituted Carboxymethylcellulose Sodium in 400 mL of water, and during the first 30 minutes, stir for 1 minute every 10 minutes. Allow to stand for 1 hour, and centrifuge, if necessary. Decant 100.0 mL of the supernatant onto a fast filter paper in a vacuum filtration funnel, apply a vacuum, and collect 75.0 mL of the filtrate. Evaporate in a tared platinum or porcelain dish, and dry at 105° for 4 hours: not more than 70% is found.

Heavy metals, *Method II* ⟨231⟩: To the residue obtained in the test for *Residue on ignition*, add 1 mL of hydrochloric acid, evaporate on a water bath, and dissolve in 20 mL of water [NOTE—Use this solution in *Identification* test *D*.]: the limit is 20 µg per g.

Limit of sodium chloride and sodium glycolate—

SODIUM CHLORIDE—Transfer an accurately weighed quantity of about 5 g of Low-Substituted Carboxymethylcellulose Sodium to a 250-mL conical flask, add 50 mL of water and 5 mL of 30% hydrogen peroxide, and heat on a water bath for 20 minutes, stirring occasionally to ensure hydration. Cool, add 100 mL of water and 10 mL of nitric acid, and titrate, while stirring constantly with 0.05 N silver nitrate VS, determining the endpoint potentiometrically using a silver electrode and a mercurous sulfate electrode with a potassium sulfate bridge. Calculate the percentage of sodium chloride (NaCl) in the Low-Substituted Carboxymethylcellulose Sodium taken by the formula:

$$584.4VN/(100 - b)W,$$

in which 584.4 is the equivalence factor for sodium chloride; V is the volume, in mL, of silver nitrate; N is the normality of silver nitrate; b is the percentage obtained from the test for *Loss on drying*, determined separately; and W is the weight, in g, of the Low-Substituted Carboxymethylcellulose Sodium taken.

SODIUM GLYCOLATE—

Test solution—Transfer an accurately weighed quantity of about 500 mg of Low-Substituted Carboxymethylcellulose Sodium to a beaker, moisten thoroughly with 5 mL of glacial acetic acid, add 5 mL of water, and stir with a glass rod to ensure proper hydration (about 30 minutes). Add 80 mL of acetone while stirring, add 2 g of sodium chloride, and stir for several minutes to ensure the complete precipitation of carboxymethylcellulose. Filter through a fast filter paper, previously wetted with a small amount of acetone, and collect the filtrate in a 100-mL volumetric flask. Rinse the beaker and filter with acetone, and add the washings to the flask. Dilute the filtrate with acetone to volume, and mix. Allow to stand for 24 hours without shaking, and use the clear supernatant.

Standard stock solution—Transfer 100 mg of glycolic acid, previously dried overnight in a vacuum desiccator over phosphorus pentoxide and accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Standard solutions—Into four identical 100-mL volumetric flasks, transfer 0.5-mL, 1.0-mL, 1.5-mL, and 2.0-mL portions of the *Standard stock solution*, respectively. To each flask, add water to make 5 mL, add 5 mL of glacial acetic acid, dilute with acetone to volume, and mix.

Blank—Use an acetone solution containing 5% of glacial acetic acid and 5% water.

Procedure—Transfer 2.0 mL of the *Test solution* and 2.0 mL of each *Standard solution* to separate 25-mL volumetric flasks. Place the uncovered flasks in a boiling water bath to remove the acetone, remove from the bath, and allow to

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cool. To each flask, add 5.0 mL of 2,7-dihydroxynaphthalene TS, mix, add an additional 15 mL of 2,7-dihydroxynaphthalene TS, and mix again. Cover the mouth of each flask with a small piece of aluminum foil, place the flasks upright in a boiling water bath for 20 minutes, remove from the bath, cool, dilute with sulfuric acid to volume, and mix. Determine the absorbance of each solution at 540 nm with a suitable spectrophotometer against the *Blank*, and prepare a standard curve using the absorbances obtained from the *Standard solutions.* From the standard curve and the absorbance of the *Test solution*, determine the weight (*w*), in mg, of glycolic acid in the *Test solution*, and calculate the percentage of sodium glycolate in the Low-Substituted Carboxymethylcellulose Sodium taken by the formula:

$$(1.29)10w/[(100 - b)W],$$

in which 1.29 is a factor converting glycolic acid to sodium glycolate; *w* is the weight, in mg, of glycolic acid from the standard curve; *b* is the percentage obtained from the *Loss on drying* test, determined separately; and *W* is the weight, in g, of the Low-Substituted Carboxymethylcellulose Sodium taken. The sum of the percentages from the tests for *Sodium chloride* and *Sodium glycolate* is not more than 0.5%.

Content of sodium—Calculate the percentage of sodium in the Low-Substituted Carboxymethylcellulose Sodium taken by the formula:

$$0.3238A,$$

in which 0.3238 is a factor converting sodium sulfate to sodium; and *A* is the percentage obtained from the test for *Residue on ignition*, determined separately.■1S (*NF22*)

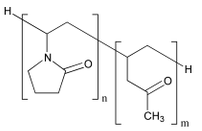
BRIEFING

Copovidone, page 948 of *PF* 28(3) [May–June 2002]. This new monograph, which previously appeared in *Pharmacopeial Previews*, is now forwarded to *In-Process Revision*. It is proposed to revise the current *Packaging and storage* statement to incorporate specifications provided by the manufacturer. Editorial style changes have also been made.

(EMC: C. Sheehan; PSD: C. Okeke) RTS—39919-1

Add the following:

■Copovidone



$(C_6H_9NO)_n + (C_4H_6O_2)_m$

Acetic acid ethenyl ester polymer with 1-ethenyl-2-pyrrolidone.

1-Vinyl-2-pyrrolidone polymer with vinyl acetate [*25086-89-9*].

» Copovidone is a copolymer of 1-vinyl-2-pyrrolidone and vinyl acetate in the mass proportion of 3:2. The nominal K-value of Copovidone as stated in the labeling is not less than 90.0 percent and not more than 110.0 percent.

Packaging and storage—Preserve in tight containers, protected from moisture. Store at 25°, excursion permitted up to 40°.

Labeling—Label it to indicate its nominal K-value.

USP Reference standards ⟨11⟩—*USP Copovidone RS.*

Clarity and color of solution—Dissolve 1.0 g in 10 mL of water: the solution is clear or slightly opalescent and colorless to pale yellow or pale red.

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Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: To 5 mL of a solution (1 in 50) add a few drops of iodine TS: a deep red color is produced.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 5.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Limit of aldehydes—

Phosphate buffer—Transfer 8.7 g of monobasic potassium phosphate to a 500-mL volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N potassium hydroxide to a pH of 9.0, dilute with water to volume, and mix.

Aldehyde dehydrogenase solution—Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, dissolve in 10.0 mL of water, and mix. [NOTE—This solution is stable for 8 hours at 4°.]

NAD solution—Transfer 40 mg of nicotinamide adenine dinucleotide to a glass vial, dissolve in 10.0 mL of *Phosphate buffer*, and mix. [NOTE—This solution is stable for 4 weeks at 4°.]

Blank solution—Use water.

Standard solution—Transfer about 2 mL of water at 4° to a glass weighing bottle, and weigh accurately. Add about 100 mg of freshly distilled acetaldehyde, and weigh accurately. Transfer this solution to a 100-mL volumetric flask. Rinse the weighing bottle with several portions of water at 4°, and transfer each rinsing to the 100-mL volumetric flask. Dilute the solution in the 100-mL volumetric flask with water at 4° to volume. Store at 4° for about 20 hours. Pipet 1 mL of this solution into a 100-mL volumetric flask, dilute with *Phosphate buffer* to volume, and mix.

Test solution—Transfer about 1 g of Copovidone, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Phosphate buffer*, dilute with *Phosphate buffer* to volume, and mix. Insert a stopper into the flask, heat at 60° for 1 hour, and cool to room temperature.

Procedure—Pipet 0.5 mL each of the *Standard solution*, the *Test solution*, and the *Blank solution* into separate 1-cm cells. Add 2.5 mL of *Phosphate buffer* and 0.2 mL of *NAD solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2 to 3 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm. Add 0.05 mL of *Aldehyde dehydrogenase solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm. Calculate the percentage of aldehydes, expressed as acetaldehyde, in the portion of Copovidone taken by the formula:

$$10(C/W)\left[\frac{(A_{U2}-A_{U1})-(A_{B2}-A_{B1})}{(A_{S2}-A_{S1})-(A_{B2}-A_{B1})}\right],$$

in which C is the concentration, in mg per mL, of acetaldehyde in the *Standard solution; W* is the weight, in g, calculated on the dried basis, of Copovidone taken to prepare the *Test solution;* A_{U1}, A_{S1}, and A_{B1} are the absorbances of the solutions obtained from the *Test solution*, the *Standard solution*, and the *Blank solution*, respectively, before the addition of the *Aldehyde dehydrogenase solution;* and A_{U2}, A_{S2}, and A_{B2} are the absorbances of the solutions obtained from the *Test solution*, the *Standard solution*, and the *Blank solution*, respectively, after addition of the *Aldehyde dehydrogenase solution:* not more than 0.05% is found.

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Limit of hydrazine—

Standard solution—Dissolve ~~an~~ accurately weighed ~~quantity~~ quantities of salicylaldazine and salicylaldehyde in toluene, and dilute quantitatively, and stepwise if necessary, with toluene to obtain a solution having ~~a~~ known concentrations of 9 µg and 10 mg per mL, respectively.

Test solution—Transfer the equivalent of 2.5 g of dried Copovidone, accurately weighed, to a 50-mL centrifuge tube, add 25 mL of water, and mix to dissolve. Add 500 µL of a 1 in 20 solution of salicylaldehyde in methanol, adjust the solution with 0.25 N sulfuric acid to a pH of about 2, swirl, and heat in a water bath at 60° for 15 minutes. Allow to cool, add 2.0 mL of toluene, insert a stopper in the tube, shake vigorously for 2 minutes, and centrifuge. Use the clear upper toluene layer as the *Test solution.*

Procedure—Separately apply 10 µL of the *Test solution* and the *Standard solution* to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of dimethylsilanized chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatogram in a solvent system consisting of a mixture of ~~methanol and water (2:1)~~ acetonitrile and water (85:15) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by examination under UV light at a wavelength of 365 nm: salicylaldazine appears as a fluorescent spot having an R_F value of about ~~0.3,~~ 0.6 to 0.7, and the fluorescence of any salicylaldazine spot from the *Test solution* is not more intense than that produced by the spot obtained from the *Standard solution:* not more than 1 µg per g is found.

Limit of peroxides—

Copovidone solution—Transfer the equivalent of 2.0 g of dried Copovidone, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test solution—Transfer 25.0 mL of *Copovidone solution* to a 50-mL beaker, add 2 mL of titanium trichloride–sulfuric acid TS, and mix. Allow to stand for 30 minutes at room temperature.

Blank solution—Transfer 25.0 mL of *Copovidone solution* to a 50-mL beaker, add 2 mL of 13% sulfuric acid, and mix.

Procedure—Determine the absorbance of the *Test solution* in a 1-cm cell at the wavelength of maximum absorbance at about 405 nm, with a suitable spectrophotometer, using the *Blank solution* as the blank: the absorbance is not more than 0.35 (corresponding to not more than 0.04%, expressed as hydrogen peroxide).

Limit of monomers—Dissolve the equivalent of 5.0 g of dried Copovidone in 20 mL of methanol, and slowly add 20.0 mL of iodobromide TS. Allow to stand for 30 minutes, protected from light, with repeated shaking. Add 5 mL of potassium iodide solution (1 in 10), and titrate the liberated iodine with 0.1 N sodium thiosulfate VS until the solution is yellow. Continue the titration dropwise until the solution is colorless. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩): the difference between the volumes of 0.1 N sodium thiosulfate consumed in the blank and the specimen titrations is not more than 0.9 mL, corresponding to not more than 0.1% of monomers calculated as vinylpyrrolidone.

K-value—Transfer an accurately weighed quantity of undried Copovidone, equivalent to about 1.0 g on the dried basis, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 1 hour. Deter-

mine the viscosity, using a capillary-tube viscosimeter (see *Viscosity* ⟨911⟩), of this solution at 25 ± 0.2°. Calculate the K-value of Copovidone by the formula:

$$\frac{\sqrt{300c\log z+(c+1.5c\log z)^2}+1.5c\log z-c}{0.15c+0.003c^2},$$

in which c is the weight, in g, on the dried basis, of the specimen tested in each 100.0 mL of solution, and z is the viscosity of the test solution relative to that of water: the K-value is not less than 90.0% and not more than 110.0% of the K-value stated on the label.

Content of copolymerized vinyl acetate—Determine the saponification value as directed for *Saponification Value* under *Fats and Fixed Oils* ⟨401⟩. Calculate the percentage of copolymerized vinyl acetate in the Copovidone taken by the formula:

$$0.1(86.09/56.11)(S),$$

in which 86.09 and 56.11 are the molecular weights of vinyl acetate and potassium hydroxide, respectively, and S is the saponification value: not less than 35.3% and not more than 41.4% of the copolymerized vinyl acetate component, calculated on the dried basis, is found.

Nitrogen, *Method II* ⟨461⟩—Proceed as directed using about 0.1 g of Copovidone, accurately weighed. In the procedure, use 5 g of a powdered mixture of potassium sulfate, cupric sulfate, and titanium dioxide (33:1:1) instead of potassium sulfate and cupric sulfate (10:1), omit the use of hydrogen peroxide, and heat until the solution has a clear, yellow-green color and the sides of the flask are free from carbonaceous material. Then heat for a further 45 minutes, add 20 mL of water, instead of 70 mL, after the second heating, and use bromocresol green–methyl red TS instead of methyl red–methylene blue TS. Titrate the distillate with 0.05 N sulfuric acid VS until the color of the solution changes from green through pale grayish blue to pale grayish red-purple: the nitrogen content, on the dried basis, is not less than 7.0% and not more than 8.0%.■1S (*NF22*)

BRIEFING

Hymetellose, page 1633 of *PF* 28(5) [Sept.–Oct. 2002]. This new monograph, which previously appeared in *Pharmacopeial Previews*, is now forwarded to *In-Process Revision*. It is proposed to add storage conditions to the *Packaging and storage* section.

(EMC: E. Gonikberg; PSD: C. Okeke) RTS—39918-1

Add the following:

■Hymetellose

Methylhydroxyethylcellulose.

Cellulose 2-hydroxyethyl methyl ether [*9032-42-2*].

» Hymetellose is a partly *O*-(methylated) and *O*-(2-hydroxyethylated) cellulose.

Packaging and storage—Preserve in well-closed containers. Store at 25°, excursion permitted between 15° and 30°. Avoid excessive heat and freezing. Protect from moisture.

Labeling—Label it to indicate the viscosity of a solution (1 in 50) at 20°.

Identification—

A: Use the solution prepared in the test for *Color of solution.* Heat the solution in a water bath while stirring: at a temperature above 50°, the solution becomes cloudy or a flocculent precipitate is formed. The solution becomes clear again on cooling.

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B: Transfer 1 mL of the solution from *Identification* test *A* to a glass plate, and allow the water to evaporate: a thin film is formed.

C: To 10 mL of the solution from *Identification* test *A*, add 0.3 mL of 2 N acetic acid and 2.5 mL of tannic acid TS: a yellowish-white, flocculent precipitate is formed that dissolves in ammonia TS.

D: In a test-tube about 160-mm long, thoroughly mix 1 g of Hymetellose with 2 g of finely powdered manganese sulfate. Introduce, to a depth of 2 cm into the upper part of the tube, a strip of filter paper impregnated with a freshly prepared *Diethanolamine–sodium nitroprusside solution.* Insert the tube 8 cm into a silicone-oil bath at 190° to 200°. The filter paper becomes blue within 10 minutes. Perform a blank test.

Diethanolamine–sodium nitroprusside solution—Prepare a sodium nitroprusside solution (1 in 20) and adjust with 1 N hydrochloric acid to a pH of 9.8. Mix 11 mL of this solution with 1 mL of a diethanolamine solution (1 in 5) in water.

E: Dissolve 0.2 g of Hymetellose completely, without heating, in 15 mL of 70% sulfuric acid. Pour the solution with stirring into 100 mL of ice water, and dilute with ice water to 250 mL. Transfer 1 mL of this solution to a test tube, and while cooling in ice water, add dropwise 8 mL of sulfuric acid, and mix thoroughly. Heat in a water bath for exactly 3 minutes, and immediately cool in ice water. While the mixture is cold, carefully add 0.6 mL of ninhydrin TS, and mix well. Allow to stand at 25°: a pink color is produced immediately and does not become violet within 100 minutes.

Color of solution—While stirring, add a portion equivalent to 1.0 g of the dried Hymetellose to 50 g of carbon dioxide-free water heated to 90°. Allow to cool, adjust the weight of the solution to 100 g with carbon dioxide-free water, and stir until dissolution is complete. This solution is not more intensely colored than a solution prepared immediately before use by mixing 2.4 mL of ferric chloride CS and 0.6 mL of cobaltous chloride CS with *Diluent* to make 10 mL, and diluting 5 mL of this solution with *Diluent* to make 100 mL. Make the comparison by viewing the substance and the solution downward in matched color-comparison tubes against a white surface (see *Color and Achromicity* ⟨631⟩).

Diluent—Dilute 27.5 mL of hydrochloric acid to 1000 mL with water.

Clarity of solution—

Hydrazine sulfate solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours before use. [*Caution—Hydrazine sulfate is highly toxic. Avoid skin contact.*]

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent mixture—[NOTE—This suspension is stable for 2 months. Mix before use, and do not use if it adheres to the container.] To the flask containing *Methenamine solution*, add 25.0 mL of *Hydrazine sulfate solution*, mix, and allow to stand for 24 hours.

Opalescence standard—[NOTE—Use this suspension within 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent mixture* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspension—Transfer 30.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Use the solution from the test for *Color of solution.*

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain

a depth of 40 mm. Similarly transfer a portion of the *Reference suspension* to a separate matching test tube. Compare the *Test solution* and the *Reference suspension* in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The *Test solution* is to be compared to the *Reference suspension* five minutes after preparation of the *Reference suspension.*] The *Test solution* is not more opalescent than the *Reference suspension.*

Viscosity ⟨911⟩—While stirring, add a portion equivalent to 6.0 g of the dried Hymetellose to 150 g of carbon dioxide-free water heated to 90°. Stir with a propeller-type stirrer for 10 minutes, place the flask in a bath of ice water, continue the stirring, and allow to remain in the bath of ice water for 40 minutes to ensure that dissolution is complete. Adjust the mass of the solution to 300 g, and centrifuge the solution to expel any entrapped air. Adjust the temperature of the solution to 20 ± 0.1°, and determine the viscosity using a rotational viscometer with a shear rate of 10 per second: the apparent viscosity is not less than 75% and not more than 140% of the value stated on the label.

pH ⟨791⟩—Use the solution from the test for *Color of solution:* the pH is between 5.5 and 8.0.

Loss on drying ⟨731⟩—Dry about 1.0 g of Hymetellose at 105° to constant weight: it loses not more than 10.0% of its weight.

Residue on ignition ⟨281⟩: not more than 1.0%, determined on 1.0 g.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Chloride ⟨221⟩—Dilute 1.0 mL of the solution from the *Color of solution* test with water to 20 mL, and add 1 mL of nitric acid and 1 mL of silver nitrate TS. Mix, allow to stand for 5 minutes protected from direct sunlight, and compare the turbidity, if any, with that produced from a 10-mL aliquot of a control (prepared by diluting 0.71 mL of 0.020 N hydrochloric acid to 100 mL) in an equal volume of total solution containing the quantities of reagents used in the test (see *Visual Comparison* in the section *Procedure*, under *Spectrophotometry and Light-Scattering* ⟨851⟩): any turbidity produced by the test specimen does not exceed that of the control preparation (0.5%).■1S (*NF22*)

BRIEFING

Hypromellose Acetate Succinate, page 142 of *PF* 29(1) [Jan.–Feb. 2003]. On the basis of comments received, it has been determined that the previously proposed *Identification* test provides adequate results for fine grades. However, granular-grade samples may be rubbery and difficult to grind to the fine powder required for high-quality spectra. It is now proposed to use a single bounce attenuated total reflectance procedure that generates high-quality spectra for both fine and granular grades. The method was validated using a Spectra-Tech Foundation Series Thunderdome ATR accessory.

It is also proposed to replace the titration methods in the tests for *Limit of free succinic acid* and *Content of succinoyl groups* and the gas chromatographic method in the test for *Content of acetyl groups* with the tests for *Limit of free acetic and succinic acids* and *Content of acetyl and succinoyl groups*, using a single liquid chromatographic method. The method is based on analyses performed with a Phenomenex Aqua C18 brand of L1 column. The typical retention times for acetic acid and succinic acid are about 3.8 minutes and 7.4 minutes, respectively.

It is also proposed to replace the gas chromatographic procedure in the test for *Content of methoxy and hydroxypropoxy groups* with a new liquid chromatographic method based on analyses performed with a Keystone Aquasil brand of L1 column. The typical retention times for methyl iodide, isopropyl iodide, and *o*-xylene are about 8.1, 13.6, and 15.6 minutes, respectively.

In addition, editorial style changes have been made.

(EMC: E. Gonikberg) RTS—39722-1

Add the following:

■Hypromellose Acetate Succinate

Hydroxypropyl methylcellulose acetate succinate.

Cellulose, 2-hydroxypropyl methyl ether, acetate hydrogen butanedioate.

Cellulose, 2-hydroxypropyl methyl ether, acetate succinate [*71138-97-1*].

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» Hypromellose Acetate Succinate is a mixture of acetic acid and monosuccinic acid esters of hydroxypropyl methylcellulose. When dried at 105° for 1 hour, it contains not less than 12.0 percent and not more than 28.0 percent of methoxy groups ($–OCH_3$), not less than 4.0 percent and not more than 23.0 percent of hydroxypropoxy groups ($–OCH_2CHOHCH_3$), not less than 2.0 percent and not more than 16.0 percent of acetyl groups ($–COCH_3$), and not less than 4.0 percent and not more than 28.0 percent of succinoyl groups ($–COC_2H_4COOH$).

Packaging and storage—Preserve in tight containers. Store at room temperature. Avoid excessive heat and freezing. Protect from moisture.

Labeling—Label it to indicate its nominal viscosity type.

USP Reference standards ⟨11⟩—*USP Hypromellose Acetate Succinate RS.*

Identification, ~~*Infrared Absorption* ⟨197K⟩, on undried specimen.~~ *Infrared Absorption* ⟨197A⟩—Do not dry specimens. Use a Fourier transform infrared spectrometer fitted with a suitable accessory for single bounce attenuated total reflectance (see *Spectrophotometry and Light-Scattering* ⟨851⟩) with a diamond crystal. Acquire a background single-beam spectrum with a clean diamond crystal sampling plate in place. Place the sample on the diamond crystal sampling surface with a microspatula or equivalent. For best results, the sample should cover the crystal surface under the pressure point tip. Using the pressure device, apply pressure to the sample, making sure the sample remains centered under the pressure tip. Acquire a single-beam spectrum of the sample, and make the necessary corrections for the background. Release the pressure device, and clear it from the sample area. Wipe the sample off the crystal and pressure device tip, and rinse both with acetone. The IR spectrum so obtained exhibits maxima only at the same wavelengths as a similarly obtained spectrum of USP Hypromellose Acetate Succinate RS.

Viscosity ⟨911⟩—

Sodium hydroxide solution—Immediately before use, dissolve 4.3 g of sodium hydroxide in carbon dioxide-free water to make 1000 mL.

Procedure—To 2.00 g of Hypromellose Acetate Succinate, previously dried, add *Sodium hydroxide solution* to make 100.0 g, stopper the vessel, and dissolve by constant shaking for 30 minutes. Adjust the temperature of the solution to 20 ± 0.1°, and determine the viscosity in a suitable viscometer, as directed for *Procedure for Cellulose Derivatives* under *Viscosity* ⟨911⟩. Its viscosity is not less than 80% and not more than 120% of that stated on the label.

Loss on drying ⟨731⟩—Dry it at 105° for 1 hour: it loses not more than 5.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.20%, determined at 600 ± 50°.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

~~**Limit of free succinic acid**—Transfer about 1.5 g of Hypromellose Acetate Succinate, previously dried at 105° for 1 hour and accurately weighed, to a separator, dissolve in 50 mL of a mixture of dehydrated alcohol and dichloromethane (3:2, v/v), add 75 mL of water with shaking, and then add 50 mL of hexane and 1 g of sodium chloride. Shake well, and separate the lower water layer. Extract the organic layer with 50 mL of water, and combine the washing and the water layer. Add 3 drops of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 5.904 mg of $C_4H_6O_4$: not more than 1.0% is found.~~

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Limit of free acetic and succinic acids—

Phosphoric acid solution—Transfer 1.0 mL of 1.25 M phosphoric acid into a 50-mL volumetric flask, and dilute with water to volume.

0.02 M Phosphate buffer—Dissolve 5.44 g of monobasic potassium phosphate in 2 L of water.

Diluent—Adjust *0.02 M Phosphate buffer* with 1 N sodium hydroxide to a pH of 7.5.

Acetic acid stock solution—Add approximately 20 mL of water to a stoppered 100-mL volumetric flask, place the flask on a balance, and tare. Transfer 2.0 mL of the glacial acetic acid to the flask, and record the weight of the acid added. Fill the flask with water to volume. Transfer 6.0 mL of this solution into a 100-mL volumetric flask, and dilute with water to volume.

Succinic acid stock solution—Accurately weigh about 130 mg of succinic acid into a 100-mL volumetric flask. Add about 50 mL of water, and swirl the contents until the succinic acid is fully dissolved. Fill the flask with water to volume.

Mobile phase—Adjust the *0.02 M Phosphate buffer* to a pH of 2.8 by dropwise addition of 6 M phosphoric acid. Filter through a 0.22-µm nylon filter.

Standard solution—Transfer 4.0 mL of the *Acetic acid stock solution* into a 25-mL volumetric flask. To the same flask, transfer 4.0 mL of the *Succinic acid stock solution*, dilute with *Mobile phase* to volume, and mix. Prepare this solution in duplicate.

Test solution—Accurately weigh about 102 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of *Diluent* to the vial, and stir the content for two hours. Then, transfer 4.0 mL of the *Phosphoric acid solution* to the same vial to bring the pH of the *Test solution* to 3 or less. Invert the vial several times to ensure complete mixing, centrifuge, and use the clear supernatant as a *Test solution*. Prepare this solution in duplicate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6 mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained between 20° to 30°. The flow rate is about 1 mL per minute, and the run time is about 15 minutes. Chromatograph the first preparation of the *Standard solution*, and record the peak responses as directed for *Procedure:* the column efficiency, determined from the succinic acid peak, is not less than 8000 theoretical plates; the tailing of this peak is between 0.9 and 1.5; and the relative standard deviation for six replicate injections is not more than 2.0% for each peak. Chromatograph the second preparation of the *Standard solution:* the difference in peak areas between the two standard solutions for both acetic and succinic acid peaks does not exceed 2%. [NOTE—After each run sequence, the column should be flushed first by 50% water and 50% acetonitrile for 60 minutes and then by 100% methanol for 60 minutes. The column should be stored in 100% methanol.]

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas corresponding to acetic and succinic acids. Calculate the percentage of free acetic acid, A_{free}, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$0.0768(W_A / W)(R_{UA} / R_{SA}),$$

in which W_A is the weight of glacial acetic acid, in mg, used to prepare the *Acetic acid stock solution; W* is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the *Test solution;* and R_{UA} and R_{SA} are the peak responses for acetic acid obtained from the *Test solution* and the *Standard*

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solution, respectively. Calculate the percentage of free succinic acid, S_{free}, in the Hypromellose Acetate Succinate taken by the formula:

$$1.28(W_S / W)(R_{US} / R_{SS}),$$

in which W_S is the weight of succinic acid, in mg, used to prepare the *Succinic acid stock solution;* R_{US} and R_{SS} are the peak responses for succinic acid obtained from the *Test solution* and the *Standard solution*, respectively; and W is as defined above: the sum of free acetic acid and free succinic acid found does not exceed 1.0%.

Content of acetyl and succinoyl groups—

Mobile phase, *Standard solution*, *Acetic acid stock solution*, *Succinic acid stock solution*, *Phosphoric acid solution*, and *Chromatographic system*—Proceed as directed in the test for *Limit of free acetic and succinic acids*.

Test solution—Accurately weigh about 12.4 mg of Hypromellose Acetate Succinate into a glass vial. Transfer 4.0 mL of 1.0 N sodium hydroxide to the vial, and stir the solution for four hours. Then, add 4.0 mL of 1.25 M phosphoric acid to the same vial to bring the pH of the solution to 3 or less. Invert the test sample solution vial several times to ensure complete mixing, and filter through a 0.22-µm filter. Use the clear filtrate as the *Test solution*.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas corresponding to acetic and succinic acids. Calculate the percentage of acetic acid, *A*, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$0.0768(W_A / W_U)(R_{UA} / R_{SA}),$$

in which W_A is the weight of acetic acid, in mg, used to prepare the *Acetic acid stock solution;* W_U is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the *Test solution;* and R_{UA} and R_{SA} are the peak responses for acetic acid obtained from the *Test solution* and the *Standard solution*, respectively. Calculate the percentage of acetyl groups ($-COCH_3$) in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$0.717(A - A_{free}),$$

in which A_{free} is the percentage of free acetic acid, as determined in the test for *Limit of free acetic and succinic acid*; and *A* is as defined above. Calculate the percentage of succinic acid, *S*, in the portion of Hypromellose Acetate Succinate taken by the formula:

$$1.28(W_S / W_U)(R_{US} / R_{SS}),$$

in which W_S is the weight of succinic acid, in mg, used to prepare the *Succinic acid stock solution;* R_{US} and R_{SS} are the peak responses for succinic acid obtained from the *Test solution* and the *Standard solution*, respectively; and W_U is as defined above. Calculate the percentage of succinoyl groups ($-COC_2H_4COOH$) in the portion of Hydroxypropyl Methylcellulose Acetate Succinate taken by the formula:

$$0.856(S - S_{free}),$$

in which *S* is as defined above; and S_{free} is the percentage of free succinic acid, as determined in the test for *Limit of free acetic and succinic acids*.

~~**Content of methoxy and hydroxypropoxy groups**~~—

~~[*Caution—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the Test solution and the Standard solution in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.*]~~

~~*Hydriodic acid*—Use a reagent having a specific gravity of at least 1.69, equivalent to 55% HI.~~

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Internal standard solution—Transfer about 2.5 g of toluene, accurately weighed, to a 100-mL volumetric flask containing 10 mL of *o*-xylene, dilute with *o*-xylene to volume, and mix.

Standard solution—Into a suitable serum vial weigh about 135 mg of adipic acid and 4.0 mL of *Hydriodic acid*, pipet 4 mL of *Internal standard solution* into the vial, and close the vial securely with a suitable septum stopper. Weigh accurately the vial and contents, add 30 µL of isopropyl iodide through the septum with a syringe, weigh again, and calculate the weight of isopropyl iodide added, by difference. Similarly, add 90 µL of methyl iodide, weigh again, and calculate the weight of methyl iodide added, by difference. Shake, and allow the layers to separate.

Test solution—Transfer about 0.065 g of Hypromellose Acetate Succinate, previously dried at 105° for 1 hour and accurately weighed, to a 5-mL thick-walled reaction vial equipped with a pressure-tight septum-type closure, add an amount of adipic acid equal to the weight of the test specimen, and pipet 2 mL of *Internal standard solution* into the vial. Cautiously pipet 2 mL of *Hydriodic acid* into the mixture, immediately cap the vial tightly, and weigh accurately. Mix the contents of the vial continuously while heating at 150° for 60 minutes. Allow the vial to cool for about 45 minutes, and weigh again. If the weight loss is greater than 10 mg, discard the mixture, and prepare another *Test preparation*.

Chromatographic system—The gas chromatograph is equipped with a thermal conductivity detector and a 4-mm × 1.8-m glass column packed with 20% liquid phase G28 on 100- to 120-mesh support SIC that is not silanized. Helium is used as the carrier gas, and the temperature of the column is maintained at 130°. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times of methyl iodide, isopropyl iodide, toluene, and *o*-xylene are approximately 1.0, 2.2, 3.6, and 8.0, respectively; and the resolution, *R*, between the toluene and isopropyl iodide peaks is not less than 2.0.

Calibration—Inject about 2 µL of the upper layer of the *Standard solution* into the gas chromatograph, and record the chromatograms. Calculate the relative response factor, F_M, of equal weights of toluene and methyl iodide taken by the formula:

$$Q_M / R_{SM},$$

in which Q_M is the quantity ratio of methyl iodide to toluene in the *Standard solution*, and R_{SM} is the peak area ratio of methyl iodide to toluene obtained from the *Standard solution*. Similarly, calculate the relative response factor, F_I, of equal weights of toluene and isopropyl iodide taken by the formula:

$$Q_I / R_{SI},$$

in which Q_I is the quantity ratio of isopropyl iodide to toluene in the *Standard solution*, and R_{SI} is the peak area ratio of isopropyl iodide to toluene obtained from the *Standard solution*.

Procedure—Inject about 2 µL of the upper layer of the *Test solution* into the gas chromatograph, and record the chromatograms. Calculate the percentage of methoxy groups (−OCH_3) in the portion of Hypromellose Acetate Succinate taken by the formula:

$$2(31/142)F_M R_{UM}(W_I / W_U),$$

in which 31/142 is the ratio of the formula weights of the methoxy group and methyl iodide; F_M is defined under *Calibration*; R_{UM} is the ratio of the area of the methyl iodide peak to that of the toluene peak obtained from the *Test solution*; W_I is the weight, in g, of toluene used to prepare the *Internal standard solution*; and W_U is the weight, in g, of

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~~Hypromellose Acetate Succinate taken to prepare the *Test solution*. Similarly, calculate the percentage of hydroxypropoxy groups (–$OCH_2CHOHCH_3$) in the portion of Hypromellose Acetate Succinate taken by the formula:~~

~~$$2(75/170)F_xR_{xs}(W_x/W_s),$$~~

~~in which 75/170 is the ratio of the formula weights of the hydroxypropoxy group and isopropyl iodide; F_x is defined under *Calibration*; R_{xs} is the ratio of the area of the isopropyl iodide peak to that of the toluene peak obtained from the *Test solution*; W_x is the weight, in g, of toluene used to prepare the *Internal standard solution*; and W_s is the weight, in g, of Hypromellose Acetate Succinate taken to prepare the *Test solution*.~~

~~**Content of succinoyl groups**—Transfer about 1 g of Hypromellose Acetate Succinate, previously dried at 105° for 1 hour and accurately weighed, to a conical flask, dissolve in 50 mL of a mixture of alcohol, acetone, and water (2:2:1, v/v), add 2 drops of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination, and make any necessary corrections. Calculate the percentage of succinoyl groups by the formula:~~

~~$$(1.0108V/W) - 1.7120S,$$~~

~~in which V is the volume, in mL, of 0.1 N sodium hydroxide consumed after correction for the blank; W is the weight, in g, of Hypromellose Acetate Succinate taken; and S is the percentage of free succinic acid found as directed in the test for *Limit of free succinic acid*.~~

~~**Content of acetyl groups**—~~

~~*Apparatus*—Use the apparatus illustrated in *Figure 1*.~~

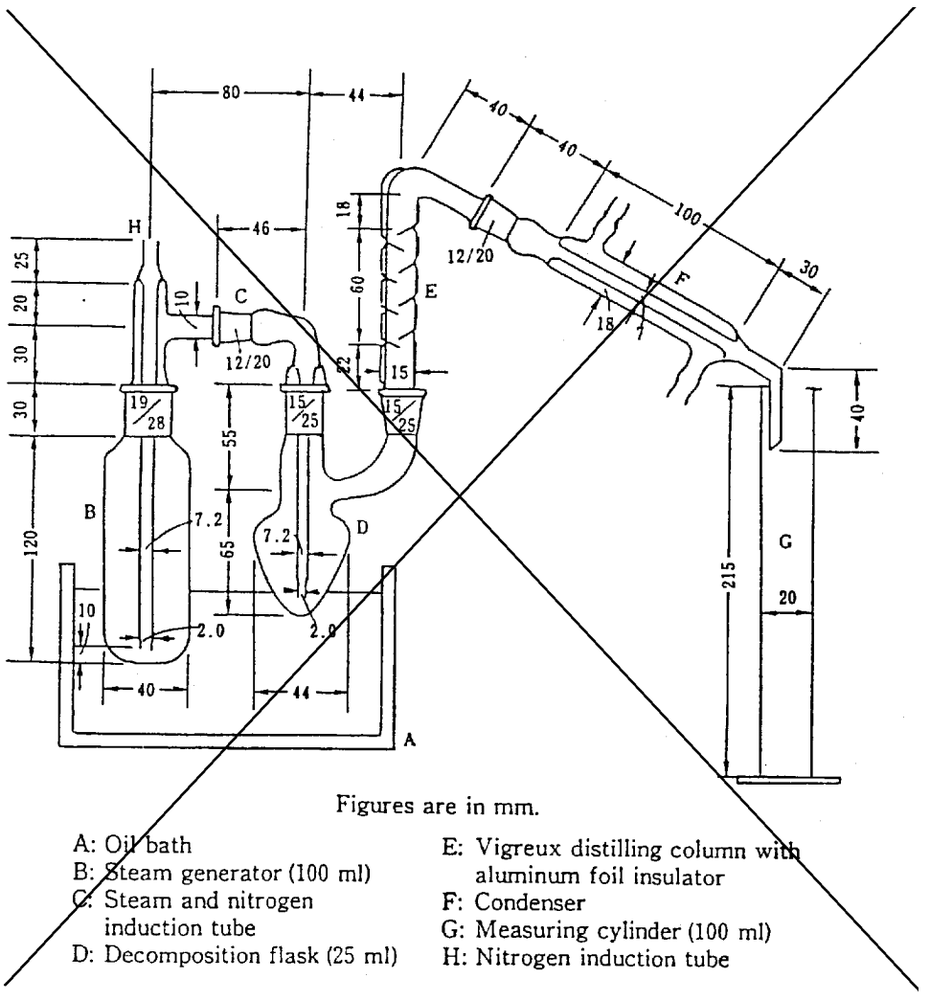

Figure 1: Apparatus for Determination of Content of Acetyl Groups

Internal standard solution—Transfer 1.0 mL of propionic acid into a 250-mL volumetric flask, and dilute with *Diluent* to volume.

Diluent—Use diluted phosphoric acid (1 in 5000).

Standard solution—Transfer about 100 mg of glacial acetic acid, accurately weighed, into a 100-mL volumetric flask, and dilute with *Diluent* to volume. Transfer 15 mL of this solution to another 100-mL volumetric flask, add 5.0 mL of the *Internal standard solution*, and dilute with *Diluent* to volume.

Test solution—Transfer about 150 mg of Hypromellose Acetate Succinate, previously dried at 105° for 1 hour and accurately weighed, to decomposition flask D, add 5 mL of sodium hydroxide TS, dissolve by shaking, and decompose in a water bath at 60° for 2 hours. After cooling, add 5 mL of diluted phosphoric acid (1 in 6), and immediately construct the apparatus as shown in Figure 1. Dip the decomposition flask and steam generator B in the oil bath at 155°, while passing nitrogen from nitrogen induction tube H at a rate of 1 to 2 bubbles per second, continue the distillation at the same temperature, and collect the distillate in measuring cylinder G. Take 60 mL of the distillate, wash the inside of

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~~condenser F with 10 mL of water, combine the washing with the distillate in a 100-mL volumetric flask, add 5.0 mL of the *Internal standard solution*, and dilute with water to volume.~~

~~*Chromatographic system*—The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 2-m glass column packed with 60- to 80-mesh support S2. The carrier gas is helium, and the temperature of the column is maintained at 180°. Adjust the flow rate so that the internal standard peak elutes in about 5 minutes. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the elution order is acetic acid, followed by the internal standard peak. The resolution, *R*, between these peaks is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0% for each of the two peaks.~~

~~*Procedure*—Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the ratio, R_U, of the area of the acetic acid peak to the area of the internal standard peak in the chromatogram obtained from the *Test solution*, and similarly calculate the ratio, R_S, in the chromatogram obtained from the *Standard solution*. Calculate the percentage of acetyl groups (–$COCH_3$) in the portion of Hypromellose Acetate Succinate taken by the formula:~~

$$(R_U / R_S)(W_S / W) \times 0.15 \times 71.68,$$

~~in which W_S is the weight, in mg, of glacial acetic acid used to prepare the *Standard solution; W* is the weight, in mg, of the portion of Hypromellose Acetate Succinate taken; and the other terms are as defined therein.~~

Content of methoxy and 2-hydroxypropoxy groups—[*Caution—Hydriodic acid and its reaction byproducts are highly toxic. Perform all steps in the preparation of the Test solution and the Standard solution in a properly functioning hood. Specific safety practices to be followed are to be identified to the analyst performing this test.*]

Hydriodic acid—Use a reagent having a specific gravity of at least 1.69, equivalent to 55% hydrogen iodide.

Solution A—Prepare a mixture of water and methanol (90:10).

Solution B—Prepare a mixture of methanol and water (85:15).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer 2 mL of *o*-xylene into a stoppered 10-mL volumetric flask, place the flask on a balance, and tare. Add about 200 µL of methyl iodide, stopper the flask, and accurately weigh: the weight of methyl iodide is about 350 mg. Tare the flask again, add about 34 µL of isopropyl iodide, and accurately weigh the flask: the recorded weight of isopropyl iodide is about 50 mg. Dilute with *o*-xylene to volume, and mix.

Standard solution—Transfer about 85 mg of adipic acid into an 8-mL vial (or other suitable container), add 2 mL of *Hydriodic acid*, and add 2.0 mL of the *Standard stock solution*. Shake and allow the phases to separate. Carefully transfer approximately 1.5 mL of the *o*-xylene (top) layer to a small vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 mL of this solution into a 10-mL volumetric flask, and dilute with methanol to volume. [NOTE—This solution is stable for 8 hours at 5°.]

Test solution—Accurately weigh about 65 mg of Hypromellose Acetate Succinate into a 5-mL reaction vial, add 2.0 mL of *o*-xylene and about 100 mg of adipic acid. Add 2.0 mL of *Hydriodic acid*, and close the vial tightly with a cap. [*Caution—Use a cap that has a top safety relief valve, such*

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as a Minniert valve, to prevent accidental explosion of the vial under high pressure when heated.] Weigh the vial before heating, and place the vial into a heating block at 150°. Shake the vial after 5 minutes and after 30 minutes of heating. Remove the vial from the heating block after 1 hour of heating, and cool. Weigh the vial. If the weight loss is greater than 10 mg, discard the mixture, and prepare another reaction solution. Carefully transfer approximately 1.5 mL of the top *o*-xylene layer into a small glass vial, making sure that the bottom aqueous layer is not disturbed. Transfer 1.0 ml of this solution into a 10-mL volumetric flask, and dilute to volume with methanol. [NOTE—This solution is stable for 8 hours at 5°.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6 mm × 15-cm column that contains 5-µm packing L1. The column temperature is maintained at 30°. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0.00	70	30	equilibration
0→8.00	70→40	30→60	linear gradient
8.00→10.00	40→15	60→85	linear gradient
10.00→17.00	15	85	isocratic

[NOTE—These gradient elution times are established on an HPLC system with a dwell volume of approximately 2.0 mL. The injection time can be adjusted relative to the start of a run to accommodate the change in dwell volume from one HPLC system to another to achieve the separation described.] Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the column efficiency, determined from the methyl iodide peak, is not less than 10,000 theoretical plates; the tailing factor of this peak is between 0.9 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0% for each peak.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas corresponding to methyl iodide and isopropyl iodide. Calculate the percentage of methoxy groups ($-OCH_3$) in the portion of Hypromellose Acetate Succinate taken by the formula:

$$4.38(W_M / W)(R_{UM} / R_{SM}),$$

in which W_M is the weight of methyl iodide, in mg, used to prepare the *Standard stock solution;* W is the weight of Hypromellose Acetate Succinate, in mg, used to prepare the *Test solution;* and R_{UM} and R_{SM} are the peak responses for methyl iodide obtained from the *Test solution* and the *Standard solution*, respectively. Calculate the percentage of 2-hydroxypropoxy groups ($-OCH_2CHOHCH_3$) in the portion of Hypromellose Acetate Succinate taken by the formula:

$$8.84(W_I / W)(R_{UI} / R_{SI}),$$

in which W_I is the weight of isopropyl iodide, in mg, used to prepare the *Standard stock solution;* R_{UI} and R_{SI} are the peak responses for methyl iodide obtained from the *Test solution* and the *Standard solution*, respectively; and W is as defined above.■1S (*NF22*)

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BRIEFING

Maltitol Solution, *NF 21* page 2789 and page 146 of *PF* 29(1) [Jan.–Feb. 2003]; **Sorbitol,** *NF 21* page 2841 and page 152 of *PF* 29(1) [Jan.–Feb. 2003]; **Sorbitol Solution,** *USP 26* page 1707 and page 114 of *PF* 29(1) [Jan.–Feb. 2003]; **Noncrystallizing Sorbitol Solution,** *NF 21* page 2842 and page 156 of *PF* 29(1) [Jan.–Feb. 2003]; **Anhydrized Liquid Sorbitol,** page 154 of *PF* 29(1) [Jan.–Feb. 2003]. These monographs are being presented again with editorial changes to the tests for *Reducing sugars* and *Limit of nickel*. It is proposed to remove the cross-reference to the *Mannitol* monograph for the tests for *Reducing sugars* and *Limit of nickel*. The *In-Process Revision* proposal for the *Mannitol* monograph first appeared on page 3017 of *PF* 27(5) [Sept.–Oct. 2001].

(EMC: C. Sheehan) RTS—39694-1

Change to read:

» Maltitol Solution is a water solution ~~of a hydrogenated, partially hydrolyzed starch. It contains,~~

▲containing,▲*NF22*
on the anhydrous basis, not less than 50.0 percent of D-maltitol ($C_{12}H_{24}O_{11}$) (w/w), and not more than ~~16.0~~

▲8.0▲*NF22*
percent of D-sorbitol ($C_6H_{14}O_6$) (w/w). The amounts of total sugars, other polyhydric alcohols, and any polyol anhydrides, if detected, are not included in the requirements nor

▲in▲*NF22*
the calculated amount under *Other Impurities*.

Change to read:

Packaging and storage— ~~Preserve in tight containers.~~

▲Preserve in well-closed containers. Do not store below 20°.▲*NF22*

Change to read:

Identification—

A: ~~— *Developing solvent*— Prepare a mixture of *n* propyl alcohol, ethyl acetate, and water (70:20:10).~~

~~*Standard solution*— Dissolve USP Maltitol RS in water to obtain a solution having a concentration of 2.5 mg per mL.~~

~~*Test solution*— Dilute Maltitol Solution with water to obtain a solution containing, on the anhydrous basis, about 2.5 mg of maltitol per mL.~~

~~*Procedure*— Apply separately 2 µL each of the *Standard solution* and the *Test solution* to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel. Allow the spots to dry, and develop the plate in a developing chamber containing the *Developing solvent* until the solvent front has moved about 17 cm. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. Spray the plate with sodium metaperiodate solution (1 in 500), air-dry for 15 minutes, spray with a 1 in 50 solution of 4,4′-tetramethyldiaminodiphenylmethane in a mixture of acetone and glacial acetic acid (4:1), and wait for 30 minutes to bring out the full color of the spots: the principal spot obtained from the *Test solution* corresponds in R_f value and color to that obtained from the *Standard solution*.~~

▲Dissolve 1.4 g of Maltitol Solution in 75 mL of water. Transfer 3 mL of this solution to a 15-cm test tube, add 3 mL of freshly prepared catechol solution (1 in 10), and mix. Add 6 mL of sulfuric acid, mix, and gently heat the tube in a flame for about 30 seconds: a deep pink or wine red color appears.▲*NF22*

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

Add the following:

▲**Microbial limits** ⟨61⟩—The total aerobic microbial count using the *Plate Method* is not more than 10^3 cfu per mL, and the total combined molds and yeasts count is not more than 10^2 cfu per mL.▲*NF22*

Add the following:

▲**pH** ⟨791⟩: between 5.0 and 7.5, in a 14% (w/w) solution of Maltitol Solution in carbon dioxide-free water.▲*NF22*

Change to read:

Water, *Method I* ⟨921⟩: not more than ~~30.0%.~~

▲31.5%.▲*NF22*

Change to read:

Residue on ignition ⟨281⟩: not more than 0.1%,

▲calculated on the anhydrous basis, determined on a 2-g portion, accurately weighed.▲*NF22*

Delete the following:

▲~~**Chloride** ⟨221⟩— A 1.5-g portion shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid (0.005%).~~▲*NF22*

Delete the following:

▲~~**Sulfate** ⟨221⟩— A 1.0-g portion shows no more sulfate than corresponds to 0.10 mL of 0.020 N sulfuric acid (0.010%).~~▲*NF22*

Delete the following:

▲~~**Heavy metals,** *Method II* ⟨231⟩: 0.001%.~~▲*NF22*

Change to read:

Reducing sugars— ~~Dilute 0.2 g with water to 2 mL. Add 5 mL of alkaline cupric citrate TS. Heat for 5 minutes in a boiling water bath: not more than a slight precipitate is formed. The amount determined in this test is not included in the calculated amount under *Other Impurities*.~~

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■To an amount of Maltitol Solution, equivalent to 3.3 g on the anhydrous basis, add 3 mL of water, 20.0 mL of cupric citrate TS, and a few glass beads. ~~Proceed as directed in the test for *Reducing sugars* under *Mannitol*, beginning with "Heat so that boiling begins."~~ Heat so that boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS using 2 mL of starch TS, added towards the end of the titration, as an indicator. Not less than 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to not more than 0.3% of reducing sugars, on the anhydrous basis, as glucose. The amount determined in this test is not included in the calculated amount under *Other Impurities*.■1S (*NF22*)

Add the following:

■**Limit of nickel**—Proceed as directed in the test for *Limit of nickel* under *Sorbitol Solution*. Not more than 1 µg per g, calculated on the anhydrous basis, is found.■1S (*NF22*)

Change to read:

Assay—

Mobile phase—Use degassed water.

Standard preparation—Dissolve accurately weighed quantities of USP Maltitol RS and USP Sorbitol RS in water~~, and dilute quantitatively with water to obtain a solution having known concentrations of about 10.0 mg of maltitol and 1.6 mg of sorbitol per mL.~~

▲to obtain a solution having known concentrations of about 10 mg per g and 1.6 mg per g, respectively.▲*NF22*

Assay preparation—~~Transfer about 1 g of Solution, accurately weighed, to a 50-mL volumetric flask, dilute with water to volume, and mix.~~

▲Accurately weigh about 0.4 g of Maltitol Solution, and dissolve in and dilute with water to about 20 g. Accurately record the final solution weight, and mix thoroughly.▲*NF22*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector that is maintained at a constant temperature ~~and a 9-mm × 30-cm column that contains packing L19. The column temperature is maintained at 85 ± 0.5°,~~ ▲of about 35° and a 7.8-mm × 10-cm column that contains packing L34. The column temperature is maintained at a constant temperature of about 60°, controlled to within ± 2°,▲*NF22* and the flow rate is about 0.5 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:*

▲the relative retention times are about 0.38 for maltotriitol, 0.48 for maltitol, and 1.0 for sorbitol; the tailing factor for maltitol▲*NF22* and sorbitol▲*NF22* is not more than 1.2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about ~~20 µL~~ ▲10 µL)▲*NF22* of the *Assay preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. ~~The elution pattern includes a broad band, starting from the void volume, that includes the higher molecular weight hydrogenated polysaccharides, followed by 3 individual peaks representing maltotriitol, maltitol, and sorbitol. The relative retention times are about 0.45 for maltotriitol, 0.6 for maltitol, and 1.0 for sorbitol. Separately calculate the quantities, in mg, of sorbitol and maltitol in the portion of Solution taken by the formula:~~

~~$$50C(r_U/r_S),$$~~

~~in which C is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard preparation*~~

▲Separately calculate the percentages, ~~of maltitol and sorbitol~~ on the anhydrous basis, of D-maltitol and D-sorbitol in the portion of Maltitol Solution taken by the formula:▲*NF22*

~~$$100(C_S/C_U)(r_U/r_S),$$~~

▲$$[10{,}000(C_S/C_U)(r_U/r_S)]/(100–W),$$

in which C_S is the concentration, in mg per g, of the appropriate USP Reference Standard in the *Standard preparation;* ~~, calculated on the anhydrous basis~~ C_U is the concentration, in mg per g, of ~~the corresponding analyte~~ Maltitol Solution in the *Assay preparation;* ~~, calculated on the anhydrous basis; and~~▲*NF22* r_U and r_S are the peak responses of the corresponding analyte obtained from the *Assay preparation* and the *Standard preparation*, respectively;

▲and W is the percentage obtained in the test for *Water*.▲*NF22*

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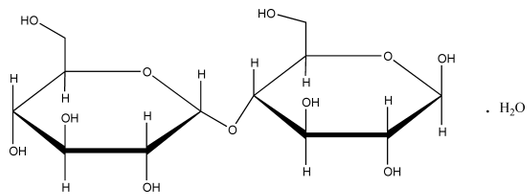
BRIEFING

Maltose, page 148 of *PF* 29(1) [Jan.–Feb. 2003]. This new monograph is being presented again with changes to the *Chromatographic system* under the *Assay.* It is proposed to add a flow rate and remove the resolution requirement of not less than 4.0 between maltose and glucose given that the method already specifies the relative retention times for the product components and requires the resolution to be at least 1.6 for maltotriose/maltose. Also see briefing under *Chromatography* ⟨621⟩.

(EMC: C. Sheehan; HDQ: M. Marques) RTS—39933-1; 39943-2

Add the following:

■Maltose



$C_{12}H_{22}O_{11} \cdot H_2O$ 360.31

and $C_{12}H_{22}O_{11}$ 342.30

4-*O*-α-D-Glucopyranosyl-β-D-glucopyranose.

» Maltose is a sugar. It contains one molecule of water of hydration or is anhydrous. It contains not less than 92.0 percent of maltose, calculated on the anhydrous basis. The amounts of other sugars, if detected, are not included in the requirements or the calculated amount under *Other Impurities.*

Packaging and storage— ~~Preserve in tight containers.~~ Preserve in well-closed containers. Store at room temperature.

USP Reference standards ⟨11⟩—*USP Maltose Monohydrate RS.*

Identification—

A: Add 2 to 3 drops of a solution of Maltose (1 in 20) to 5 mL of hot alkaline cupric tartrate TS. A red precipitate is formed.

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

pH ⟨791⟩—Prepare a 1 in 10 solution in carbon dioxide-free water. For the anhydrous form, it is between 3.7 and 4.7 and for the monohydrate form, it is between 4.0 and 5.5.

Water, *Method I* ⟨921⟩—The anhydrous form contains not more than 1.5%. The monohydrate form contains not less than 5.0% and not more than 6.5%.

Residue on ignition ⟨281⟩: not more than 0.05%, determined on a 2-g portion, accurately weighed.

Heavy metals, *Method I* ⟨231⟩: not more than 5 µg per g.

Dextrin, starch, and sulfite—Dissolve 1.0 g of Maltose in 10 mL of water, and add 1 drop of iodine TS: a yellow color develops. Then add 1 drop of starch TS to this portion: a blue color develops.

Assay—

Mobile phase—Use degassed water.

Resolution solution—Dissolve accurately weighed quantities of maltotriose, maltose, and glucose in water, to obtain a solution having concentrations of about 10 mg of each per g.

Standard preparation—Dissolve an accurately weighed quantity of USP Maltose Monohydrate RS in water, to obtain a solution having a concentration~~s~~ of about 10 mg ~~of each~~ per g. Calculate the exact concentration on the anhydrous basis.

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Assay preparation—Dissolve about 0.10 g of Maltose, accurately weighed, in water, and dilute with water to about 10 g. Accurately record the final solution weight, and mix thoroughly.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatographic system is equipped with a refractive index detector maintained at a constant temperature of about 40°, and a 7.8-mm × 30-cm column that contains packing ~~L54~~ L## (See *Chromatography* ⟨621⟩). The column temperature is maintained at about 80°, controlled to within ± 2°. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure*. Adjust the flow rate to about 0.35 mL per minute such that the resolution, *R*, between maltotriose and maltose is not less than 1.6. ~~and that between maltose and glucose is not less than 4.0.~~ Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for maltotriose, 1.0 for maltose, and 1.2 for glucose; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of Maltose on the anhydrous basis, taken by the formula:

$$[10{,}000(C_S / C_U)(r_U / r_S)]/(100 - W),$$

in which C_S is the concentration, in mg per g, on the anhydrous basis of USP Maltose Monohydrate RS in the *Standard preparation;* C_U is the concentration, in mg per g, of Maltose in the *Assay preparation;* r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively; and *W* is the percentage obtained in the test for *Water*.■1S (*NF22*)

BRIEFING

Oral Solution Vehicle, page 1998 of *PF* 28(6) [Nov.–Dec. 2002]; **Oral Solution Vehicle Sugar Free,** page 1998 of *PF* 28(6) [Nov.–Dec. 2002]; **Oral Suspension Vehicle,** page 1999 of *PF* 28(6) [Nov.–Dec. 2002]. These proposed new monographs, which previously appeared in *Pharmacopeial Previews*, are now being forwarded, with changes, to *In-Process Revision*. These are monographs on vehicles, containing no therapeutic ingredients, that are provided for use in compounding pharmaceuticals. Thus, the monographs are proposed for inclusion in the *National Formulary.*

The monograph titles now proposed were adopted by the Expert Committee on Nomenclature and Labeling. The first term in the names, "Vehicle," identifies the article as a compounding medium, and the following terms, "for Oral Solution" and "for Oral Suspension," are used so that the intended function might be better understood. The addition of a *pH* specification is recommended as necessary to provide a target for the adjustment of pH, if necessary, that is specified in the compounding directions.

(CRX: C. Okeke; NL: C. Barnstein) RTS—39822-3

Add the following:

■~~Oral Solution Vehicle~~ Vehicle for Oral Solution

» Prepare ~~Oral Solution Vehicle~~ Vehicle for Oral Solution as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Sucrose	80 g
Glycerin	5 g
Sorbitol	5 g
Sodium Phosphate, Dibasic	120 mg
Citric Acid	200 mg
Potassium Sorbate	100 mg
Methylparaben	100 mg
Purified Water, a sufficient quantity to make	100 mL

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Calculate the quantity of each ingredient required for the total amount to be prepared. Accurately weigh/measure each ingredient. Heat about 30 mL of Purified Water to 70° to 75°. Add the Glycerin and Methylparaben, and stir until the Methylparaben is dissolved. Add the dibasic sodium phosphate, Citric Acid, Potassium Sorbate, and Sorbitol, and mix well. Add the Sucrose, and mix until dissolved; remove from the heat, and allow to cool. Add sufficient Purified Water to volume, and mix well. Adjust the pH if necessary. Package, and label.

Packaging and storage—Package in a tight, light-resistant container, and store at controlled room temperature.

Labeling—Label it to indicate that it is for use in compounding oral solutions and suspensions.

pH ⟨791⟩: an apparent pH between 4.0 and 5.0.

~~**Stability:**~~ **Beyond-use date:** ~~a beyond-use date of~~ not more than 6 months after preparation. A beyond-use date of more than 6 months may be assigned if supporting stability data exist. (See *Stability Criteria and Beyond-Use Dating* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩.)■1S (*NF22*)

BRIEFING

Oral Solution Vehicle Sugar Free, page 1998 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Oral Solution Vehicle*.

(CRX: C. Okeke; NL: C. Barnstein) RTS—39822-4

Add the following:

■~~Oral Solution Vehicle Sugar Free~~ Vehicle for Oral Solution, Sugar Free

» Prepare ~~Oral Solution Vehicle Sugar Free~~ Vehicle for Oral Solution, Sugar Free as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Xanthan Gum	50 mg
Glycerin	10 mL
Sorbitol Solution	25 mL
Saccharin Sodium	100 mg
Citric Acid Monohydrate	1.5 g
Sodium Citrate	2 g
Methylparaben	100 mg
Potassium Sorbate	100 mg
Purified Water, a sufficient quantity to make	100 mL

Calculate the quantity of each ingredient required for the total amount to be prepared. Accurately weigh/measure each ingredient. Heat about

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60 mL of water to about 70° to 75°. Add the Methylparaben, and stir until dissolved. Remove from the heat, and add the Glycerin, Sorbitol Solution, Saccharin Sodium, Citric Acid Monohydrate, Sodium Citrate, Potassium Sorbate, and Xanthan Gum. Add sufficient Purified Water to volume, and mix well. Adjust the pH if necessary. Package, and label.

Packaging and storage—Package in a tight, light-resistant container, and store at controlled room temperature.

Labeling—Label it to indicate that it is for use in compounding sugar-free oral solutions and suspensions.

pH ⟨791⟩: an apparent pH between 4.0 and 5.0.

Beyond-use date: ~~A beyond-use date of~~ not more than 6 months after preparation. A beyond-use date of more than 6 months may be assigned if supporting stability data exist. (See *Stability Criteria and Beyond-Use Dating* under *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩.)■IS (*NF22*)

BRIEFING

Oral Suspension Vehicle, page 1999 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Oral Solution Vehicle.*

(CRX: C. Okeke; NL: C. Barnstein) RTS—39822-5

Add the following:

■~~Oral Suspension Vehicle~~ Vehicle for Oral Suspension

» Prepare ~~Oral Suspension Vehicle~~ Vehicle for Oral Suspension as follows (see *Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).

Cellulose, Microcrystalline	800 mg
Xanthan Gum	200 mg
Carrageenan	150 mg
Carboxymethylcellulose Sodium (High Viscosity)	25 mg
Citric Acid	250 mg
Sodium Phosphate, Dibasic	120 mg
Simethicone	0.1 mL
Potassium Sorbate	100 mg
Methylparaben	100 mg
Purified water, a sufficient quantity to make	100 mL

Calculate the quantity of each ingredient required for the total amount to be prepared. Accurately weigh/measure each ingredient. Heat about 90 mL of the Purified Water to 70° to 75°. Dissolve the Methylparaben, followed by the Citric Acid, Dibasic Sodium Phosphate, and Potassium Sorbate in the heated water. Remove from the heat.

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Constantly mixing, slowly sprinkle on the Microcrystalline Cellulose, Xanthan Gum, Carrageenan, and the Carboxymethylcellulose Sodium. Continue to stir until fully hydrated, add the Simethicone, and mix well. Add sufficient Purified Water to volume, and mix well. Adjust the pH if necessary. Package, and label.

Packaging and storage—Package in a tight, light-resistant container, and store at controlled room temperature.

Labeling—Label it to indicate that it is for use in compounding oral solutions.

pH ⟨791⟩: an apparent pH between 4.0 and 5.0.

~~**Stability**~~ **Beyond-use date**—See *Beyond-use date* under ~~*Oral Solution Vehicle Sugar Free.*~~ *Vehicle for Oral Solution, Sugar Free.* ■1S (*NF22*)

BRIEFING

Peanut Oil, *NF 21* page 2805. It is proposed to modify the existing Definition to specify that the material has been processed in a manner that reduces the levels of allergenic proteins in the finished product. Since the definition of refinement varies internationally, it is proposed to include specific processes involved in producing "fully refined" oil.

(EMC: C. Sheehan) RTS—39902-1

Change to read:

» Peanut Oil is the ~~refined fixed oil~~

▪fully-refined (alkali-refined, bleached, and deodorized at 230° to 260°) oil■1S (*NF22*)
obtained from the seed kernels of one or more of the cultivated varieties of *Arachis hypogaea* Linné (Fam. Leguminosae).

BRIEFING

Polyoxyl Lauryl Ether, page 1640 of *PF* 28(5) [Sept.–Oct. 2002]; **Polyoxyl Oleate,** page 1641 of *PF* 28(5) [Sept.–Oct. 2002]; **Polyoxyl Stearyl Ether,** page 1642 of *PF* 28(5) [Sept.–Oct. 2002]. These new monographs, which previously appeared in *Pharmacopeial Previews*, are now being forwarded with minor revisions to *In-Process Revision*.

(EMC: E. Gonikberg) RTS—39918-5

Add the following:

■Polyoxyl Lauryl Ether

Polyethylene glycol monolauryl ether [*9002-92-0*].

» Polyoxyl Lauryl Ether is a mixture of the monolauryl ethers of mixed polyethylene glycols, the average polymer length being equivalent to not less than 3 and not more than 23 oxyethylene units (nominal value). It contains various amounts of free lauryl alcohol, and it may contain some free polyethylene glycols.

Packaging and storage—Preserve in tight containers, and store in a cool, dry place.

Labeling—Label it to indicate the average nominal number of oxyethylene units.

USP Reference standards ⟨11⟩—*USP Polyoxyl Lauryl Ether RS.*

Appearance of solution—Dissolve 5.0 g of Polyoxyl Lauryl Ether in 50.0 mL of alcohol, and proceed as directed for *Appearance of solution* under *Polyoxyl Stearyl Ether.*

Identification—

A: *Infrared Absorption* ⟨197F⟩—Use a thin film of melted test specimen if the material is a solid.

B: Dissolve or disperse 0.1 g in 5 mL of alcohol, add 10 mL of diluted hydrochloric acid, 5 mL of barium chloride TS, and 10 mL of phosphomolybdic acid solution (1 in 10): a precipitate is formed.

Acid value ⟨401⟩: not more than 1.0, determined on 5.0 g.

Hydroxyl value ⟨401⟩: within the ranges specified in the accompanying table.

Oxyethylene Units per Molecule (Nominal Value)	Hydroxyl Value
3	165–185
4	145–165
5	130–140
9	90–100
10	85–95
12	73–83
15	64–74
20–23	40–60

Iodine value ⟨401⟩: not more than 2.0.

Saponification value ⟨401⟩: not more than 3.0, determined on 10.0 g.

Alkalinity—Dissolve 2.0 g of Polyoxyl Lauryl Ether in a hot mixture of 10 mL of alcohol and 10 mL of water. Add 0.05 mL of bromothymol blue TS, and titrate with 0.1 N hydrochloric acid to a yellow endpoint: not more than 0.5 mL of 0.1 N hydrochloric acid is required.

Water, *Method I* ⟨921⟩: not more than 3.0%.

Total ash ⟨561⟩: not more than 0.2%, determined on 2.0 g.

Limit of free ethylene oxide and dioxane—Proceed as directed for *Limit of free ethylene oxide and dioxane* under *Polyoxyl Stearyl Ether*. Not more than 1 µg per g of free ethylene oxide is found; and not more than 10 µg per g of dioxane is found.■IS (*NF22*)

BRIEFING

Polyoxyl Stearyl Ether, page 1642 of *PF* 28(5) [Sept.–Oct. 2002]—See briefing under *Polyoxyl Lauryl Ether*.

(EMC: E. Gonikberg) RTS—39918-4

Add the following:

■Polyoxyl Stearyl Ether

Polyethylene glycol monostearyl ether [*9005-00-9*].

» Polyoxyl Stearyl Ether is a mixture of the monostearyl ethers of mixed polyethylene glycols, the average polymer length being equivalent to not less than 2 and not more than 20 oxyethylene units (nominal value). It may contain various amounts of free lauryl alcohol and some free polyethylene glycol.

Packaging and storage—Preserve in tight containers, and store in a cool, dry place.

Labeling—Label it to indicate the average nominal number of oxyethylene units.

USP Reference standards ⟨11⟩—*USP Polyoxyl Stearyl Ether RS*.

Appearance of solution—Dissolve 5.0 g of Polyoxyl Stearyl Ether in 50.0 mL of alcohol. The solution is not more intensely colored than a solution prepared immediately before use by mixing 12.0 mL of ferric chloride CS, 5.0 mL of cobaltous chloride CS, and 2.0 mL of cupric sulfate CS with dilute hydrochloric acid (10 g per liter) to make 50.0 mL, and diluting 12.5 mL of this solution with dilute hydrochloric acid (10 g per liter) to make 100.0 mL. Make

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the comparison by viewing the substance and the solution downward in matched color-comparison tubes against a white surface (see *Color and Achromicity* ⟨631⟩).

Identification—

A: *Infrared Absorption* ⟨197F⟩—Use a thin film of melted test specimen.

B: Dissolve or disperse 0.1 g in alcohol, add 10 mL of diluted hydrochloric acid, 5 mL of barium chloride TS, and 10 mL of phosphomolybdic acid solution (1 in 10): a precipitate is formed.

Acid value ⟨401⟩: not more than 1.0, determined on 5.0 g.

Hydroxyl value ⟨401⟩: within the ranges specified in the table below.

Oxyethylene Units per Molecule (Nominal Value)	Hydroxyl Value
2	150–180
10	75–90
20	40–60

Iodine value ⟨401⟩: not more than 2.0.

Saponification value ⟨401⟩: not more than 3.0, determined on 10.0 g.

Alkalinity—Dissolve 2.0 g of Polyoxyl Stearyl Ether in a hot mixture of 10 mL of alcohol and 10 mL of water. Add 0.05 mL of bromothymol blue TS, and titrate with 0.1 N hydrochloric acid to a yellow endpoint: not more than 0.5 mL of 0.1 N hydrochloric acid is required.

Water, *Method I* ⟨921⟩: not more than 3.0%.

Limit of free ethylene oxide and dioxane—[*Caution—Ethylene oxide is toxic and flammable. Prepare these solutions in a well-ventilated fume hood, using great care. Protect both hands and face by wearing polyethylene protective gloves and an appropriate face mask. Store all solutions in hermetic containers, and refrigerate at a temperature between 4° and 8°.*] [NOTE—Before using the Polyethylene Glycol 200 in this test, remove any volatile components from it by placing 500 mL of Polyethylene Glycol 200 in a 1000-mL round-bottom flask, attaching the flask to a rotary evaporator, and evaporating at a temperature of 60° and under a vacuum of 10–20 mm Hg for 6 hours.]

Acetaldehyde solution—Prepare a solution of acetaldehyde in water, containing a known concentration of about 10 µg per mL. [NOTE—Prepare the *Acetaldehyde solution* fresh just prior to use.]

Ethylene oxide stock solution—Fill a chilled pressure bottle with liquid ethylene oxide, and store in a freezer when not in use. Use a small piece of polyethylene film to protect the liquid from contact with the rubber gasket. Tare a glass-stoppered conical flask, add about 50 mL of Polyethylene Glycol 200, and reweigh the flask. Transfer about 5 mL of the liquid ethylene oxide to a 100-mL beaker chilled in a mixture of sodium chloride and wet ice (1:3). Using a gas-tight syringe that has been previously cooled to –10°, transfer about 300 µL (corresponding to about 250 mg) of liquid ethylene oxide to the Polyethylene Glycol 200, and swirl gently to mix. Replace the stopper, reweigh the flask, and determine the amount of ethylene oxide absorbed by weight difference. Adjust the weight of the mixture with Polyethylene Glycol 200 to 100.0 g, replace the stopper, and swirl gently to mix. This stock solution contains about 2.5 mg of ethylene oxide per g. [NOTE—Prepare this stock solution fresh just prior to use, and store in a refrigerator.]

Ethylene oxide solution—Tare a glass-stoppered conical flask, and chill it in a refrigerator. Add about 35 mL of Polyethylene Glycol 200, and reweigh the flask. Using a gas-tight gas chromatographic syringe that has been chilled in a refrigerator, transfer about 1 g of the chilled *Ethylene oxide stock solution*, accurately weighed, to the tared, conical

flask. Adjust the weight of the solution with Polyethylene Glycol 200 to 50.0 g, replace the stopper, and swirl gently to mix. Transfer about 10 g of this solution, accurately weighed, to a 50-mL volumetric flask. Add 30 mL of water, and mix. Dilute with water to volume, and mix to obtain a solution containing about 10 µg of ethylene oxide per mL. [NOTE—Prepare this solution fresh just prior to use, and store in a refrigerator.]

Dioxane solution—Dissolve about 1.0 g of dioxane, accurately weighed, in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 mg of dioxane per mL.

Standard solution A—Transfer 0.1 mL of *Ethylene oxide solution* to a 10-mL pressure headspace vial, add 0.1 mL of *Acetaldehyde solution* and 0.1 mL of *Dioxane solution*, seal the vial, and mix.

Standard solution B—Transfer about 1.0 g of the substance under test, accurately weighed, to another 10-mL pressure headspace vial, add 0.1 mL of *Ethylene oxide solution*, 0.1 mL of *Dioxane solution*, and 1.0 mL of *N*,*N*-dimethylacetamide. Seal the vial, and mix.

Test solution—Transfer about 1.0 g of the substance under test, accurately weighed, to a 10-mL pressure headspace vial, add 1.0 mL of *N*,*N*-dimethylacetamide and 0.2 mL of water, seal the vial, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—[NOTE—The use of a headspace apparatus that automatically transfers a measured amount of headspace is allowed.] The gas chromatograph is equipped with a flame-ionization detector, maintained at about 250°, and a 0.32-mm × 30-m glass or quartz capillary column bonded with a 1.0-µm layer of phase G1. The injection port is equipped with a split injection port with a split ratio of 20:1 and is maintained at about 150°. The column temperature is maintained at 50° for 5 minutes after injection, then programmed to increase at the rate of 5° per minute to 180°, then at the rate of 30° per minute to 230° and then maintained at 230° for 5 minutes. Each vial is heated at a temperature of 90° for 45 minutes before a suitable portion of its headspace is injected. The carrier gas is helium flowing with a linear velocity of about 20 cm per second. [NOTE—If the headspace apparatus is used, then an injection time of 12 seconds and a transfer line temperature of 150° are recommended.] Chromatograph the gaseous phase of *Standard solution A*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.94 for acetaldehyde and 1.0 for ethylene oxide; the resolution, *R*, between acetaldehyde and ethylene oxide is not less than 2.0; the dioxane peak is detected with a signal-to-noise ratio of not less than 5; and the relative standard deviation for replicate injections is not more than 15%.

Procedure—Using a heated, gas-tight gas chromatographic syringe, separately inject equal volumes (about 1 mL) of the gaseous headspace of *Standard solution B* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks: the mean areas of the ethylene oxide and dioxane peaks in the chromatogram obtained from the *Test solution* are not greater than half the mean areas of the corresponding peaks in the chromatogram obtained from *Standard solution B*. Calculate the concentration of ethylene oxide, in µg per g, in the portion of the substance under test taken by the formula:

$$Ar_U/[(r_S W_U) - (r_U W_S)],$$

in which A is the quantity, in µg, of ethylene oxide added to *Standard solution B;* r_U and r_S are the ethylene oxide peak responses obtained from the *Test solution* and *Standard solution B*, respectively; and W_U and W_S are the weights, in g, of the substance under test taken to prepare the *Test solution* and *Standard solution B*, respectively: not more than 1 µg per g is found.

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Calculate the concentration of dioxane, in µg per g, in the portion of the substance under test taken by the formula:

$$A_D r_U / 5[(r_S W_U) - (r_U W_S)],$$

in which A_D is the amount, in µg, of dioxane added to *Standard solution B;* r_U and r_S are the dioxane peak responses obtained from the *Test solution* and *Standard solution B*, respectively; and W_U and W_S are as defined above: not more than 10 µg per g is found.■1S (*NF22*)

BRIEFING

Polyoxyl Oleate, page 1641 of *PF* 28(5) [Sept.–Oct. 2002]—See briefing under *Polyoxyl Lauryl Ether*. Also, it is proposed to add storage conditions to the *Packaging and storage* section.

(EMC: E. Gonikberg; PSD: C. Okeke) RTS—39917-1

Add the following:

■Polyoxyl Oleate

Polyethylene glycol monooleate. [*9004-96-0*].

» Polyoxyl Oleate is a mixture of the monoesters and diesters of oleic acid and mixed polyethylene glycols. It may be obtained by ethoxylation of oleic acid or by esterification of polyethylene glycols with oleic acid of animal or vegetable origin. It may contain free polyethylene glycol. The average polymer length is equivalent to either 5–6 or 10 oxyethylene units (nominal values). A suitable antioxidant may be added.

Packaging and storage—Preserve in tight containers, and store in a cool, dry place. Protect from moisture.

Labeling—Label it to indicate the number of ethylene oxide units per molecule (nominal value), and the name and concentration of any added antioxidant.

USP Reference standards ⟨11⟩—*USP Polyoxyl Oleate RS*.

Identification, *Infrared Absorption* ⟨197F⟩, on undried specimen.

Acid value ⟨401⟩: not more than 1.0, determined on 10.0 g.

Hydroxyl value ⟨401⟩—See table below.

Iodine value ⟨401⟩—See table below.

Peroxide value ⟨401⟩: not more than 12.0.

Saponification value ⟨401⟩—See table below.

	5–6 Ethylene Oxide Units	10 Ethylene Oxide Units
Hydroxyl value	50–70	65–90
Iodine value	50–60	27–34
Saponification value	105–120	68–85

Fatty acid composition ⟨401⟩—Polyoxyl Oleate exhibits the following composition profile of fatty acids, as determined in the USP general chapter section *Fatty Acid Composition:*

Carbon-Chain Length	No. of Double Bonds	Percentage (%)
14	0	≤5.0
16	0	≤16.0
18	0	≤6.0
16	1	≤8.0
18	1	65.0–88.0

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Carbon-Chain Length	No. of Double Bonds	Percentage (%)
18	2	≤18.0
18	3	≤4.0
>18	—	≤4.0

Alkalinity—Dissolve 2.0 g of Polyoxyl Oleate in 20 mL of alcohol. To 2 mL of this solution, add 0.05 mL of phenol red TS: the solution is not red.

Total ash ⟨561⟩: not more than 0.3%, determined on 1.0 g.

Water, *Method I* ⟨921⟩: not more than 2.0%.

Limit of free ethylene oxide and dioxane—Proceed as directed for *Limit of free ethylene oxide and dioxane* under *Polyoxyl Stearyl Ether:* not more than 1 µg per g of free ethylene oxide is found; and not more than 10 µg per g of dioxane is found.■1S (*NF22*)

BRIEFING

Sodium Cetostearyl Sulfate. Because there is no existing *NF* monograph for this excipient, a new monograph, based on the Sodium Cetostearyl Sulfate monograph in the *European Pharmacopoeia*, *Fourth Edition*, page 1907, is being proposed.

(EMC: E. Gonikberg) RTS—39843-1

Add the following:

■Sodium Cetostearyl Sulfate

» Sodium Cetostearyl Sulfate is a mixture of sodium cetyl sulfate and sodium stearyl sulfate. It contains not less than 40.0 percent of sodium cetyl sulfate ($C_{16}H_{34}NaSO_4$), and the sum of the sodium cetyl sulfate content and sodium stearyl sulfate ($C_{18}H_{38}NaSO_4$) content is not less than 90.0 percent (both contents calculated on the anhydrous basis). It may contain a suitable buffer.

Packaging and storage—Preserve in well-closed containers. Store at temperature 25°, excursions permitted between 15° and 30°.

Labeling—Label it to indicate the name and concentration of any added buffer.

USP Reference standards ⟨11⟩—*USP Cetyl Alcohol RS*. *USP Stearyl Alcohol RS*.

Identification—

A: The retention times of the two major peaks in the chromatogram of the *Assay preparation C* correspond to those in the chromatogram of the *Resolution solution*, as obtained in the *Assay*.

B: It meets the requirements of the flame test for *Sodium* ⟨191⟩.

C: Mix 10 mg with 10 mL of ethanol, and heat to boiling on a water bath, shaking frequently. Filter immediately, and evaporate to dryness. Dissolve the residue in 7 mL of water, add 3 mL of diluted hydrochloric acid, and evaporate the solution to half its volume. Allow to cool, and filter. To the filtrate, add 1 mL of barium chloride solution (6 in 100): a white crystalline precipitate is formed.

Acidity or alkalinity—Dissolve 500 mg with heating in a mixture of 10 mL of water and 15 mL of 90% alcohol. Add 0.1 mL of phenolphthalein TS: the solution is colorless. Add 0.1 mL of 0.1 N sodium hydroxide: the solution becomes red.

Water, *Method I* ⟨921⟩: not more than 1.5%.

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Limit of sodium chloride and sodium sulfate—

Dichloroacetic acid solution—Dilute 67 mL of dichloroacetic acid to 300 mL with water, and neutralize to blue litmus paper using ammonia TS. Cool, add 33 mL of dichloroacetic acid, and dilute with water to 600 mL.

Sodium chloride—Dissolve about 5 g of Sodium Cetostearyl Sulfate, accurately weighed, in 50 mL of water, and add diluted nitric acid dropwise until the solution is neutral to blue litmus paper. Add 1 mL of potassium chromate TS, and titrate with 0.1 N silver nitrate VS, determining the endpoint potentiometrically. Calculate the percentage of sodium chloride (NaCl) in the Sodium Cetostearyl Sulfate taken by the formula:

$$5.844VN/W,$$

in which 5.844 is the equivalence factor for sodium chloride; V is the volume, in mL, of silver nitrate solution; N is the normality of silver nitrate; and W is the weight, in g, of the Sodium Cetostearyl Sulfate taken.

Sodium sulfate—Dissolve 0.5 g of Sodium Cetostearyl Sulfate, accurately weighed, in 20 mL of water, warming gently if necessary, and add 1 mL of a solution containing 0.5 g per L of dithizone in acetone. If the solution is red, add 1 N nitric acid dropwise until a bluish-green color is obtained. Add 2.0 mL of *Dichloroacetic acid solution* and 80 mL of acetone, and titrate with 0.01 M lead nitrate VS until a persistent orange-red color is obtained. Calculate the percentage of sodium chloride (Na_2SO_4) in the Sodium Cetostearyl Sulfate taken by the formula:

$$14.20VM/W,$$

in which 14.20 is the equivalence factor for sodium sulfate; V is the volume, in mL, of lead nitrate solution; M is the molarity of lead nitrate; and W is the weight, in g, of the Sodium Cetostearyl Sulfate taken. The sum of the percentages of sodium chloride and sodium sulfate is not more than 8.0%.

Limit of free cetostearyl alcohol—Examine the chromatogram of the *Assay preparation A*, obtained as directed in the *Assay*. Calculate the percentage of free cetostearyl alcohol in the Sodium Cetostearyl Sulfate taken using the formula:

$$100(A_a + B_a) \times W_{ah} / (S_{a(corr)} \times W_a),$$

in which $(A_a + B_a)$ is the sum of the areas of the cetyl alcohol and stearyl alcohol peaks in the chromatogram of the *Assay preparation A;* $S_{a(corr)}$ is defined under *Assay;* W_{ah} is the weight of the internal standard, in mg, added in the preparation of the *Assay preparation A;* and W_a is the weight, in mg, of Sodium Cetostearyl Sulfate taken to prepare the *Assay preparation A:* not more than 4.0% is found.

Assay—

Resolution solution—Dissolve accurately weighed quantities of USP Cetyl Alcohol RS and USP Stearyl Alcohol RS in alcohol to obtain a solution having a known concentration of about 5 mg of each per mL.

Internal standard solution—Prepare a solution of 1-heptadecanol in alcohol having a concentration of about 4 mg per mL.

Assay preparation A—Dissolve 300 mg of Sodium Cetostearyl Sulfate in 50 mL of alcohol, and add 2 mL of the *Internal standard solution* and 48 mL of water. Extract the solution with four 25-mL portions of pentane, adding 10-15 mL of saturated sodium chloride solution, if necessary, to facilitate the separation of the layers. Combine the organic layers, and reserve the hydro-alcoholic layers for the preparation of *Assay preparations C* and *D*. Wash the organic layer with two 30-mL portions of water, dry over anhydrous sodium sulfate, and filter.

Assay preparation B—Dissolve 300 mg of Sodium Cetostearyl Sulfate in 50 mL of alcohol, and add 50 mL of water. Extract the solution with four 25-mL portions of pentane, adding 10-15 mL of saturated sodium chloride solution, if

necessary, to facilitate the separation of the layers. Combine the organic layers, wash with two 30-mL portions of water, dry over anhydrous sodium sulfate, and filter.

Assay preparation C—Transfer 25 mL of the hydro-alcoholic solution obtained in the preparation of the *Assay preparation A* to a 200-mL flask that can be fitted with a reflux condenser. Add 20 mL of hydrochloric acid and 10 mL of the *Internal standard solution*, and boil under reflux for 2 hours. Allow to cool. Extract with four 20-mL portions of pentane. Wash the combined organic layer with two 20-mL portions of water, dry over anhydrous sodium sulfate, and filter.

Assay preparation D—Transfer 25 mL of the hydro-alcoholic solution obtained in the preparation of the *Assay preparation A* to a 200-mL flask that can be fitted with a reflux condenser. Add 20 mL of hydrochloric acid and 10 mL of alcohol, and boil under reflux for 2 hours. Allow to cool. Extract with four 20-mL portions of pentane. Wash the combined organic layer with two 20-mL portions of water, dry over anhydrous sodium sulfate, and filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.25-mm × 25-m fused silica capillary column that contains phase G2, and a split injection system with a split ratio of about 1:100. The carrier gas is nitrogen, flowing at a rate of 1 mL per minute. The column temperature is maintained at 150° at the time of injection, then programmed to increase at the rate of 5° per minute to 250°, and maintained at 250° for the duration of the analysis. The injection port and the detector temperatures are maintained at about 250°. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between cetyl alcohol and stearyl alcohol is not less than 4.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Correction for interference—Inject about 1 µL of each of the *Assay preparations A* and *B* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. If the chromatogram of the *Assay preparation B* shows a peak at the same retention time as the internal standard peak in the chromatogram of the *Assay preparation A*, calculate the ratio, *r:*

$$r = S_{cb} / S_i,$$

in which S_{cb} is the area of the cetyl alcohol peak; and S_i is the area of the peak with the same retention time as the internal standard, respectively, in the chromatogram of the *Assay preparation B*. If *r* is less than 300, calculate the corrected area, $S_{a(corr)}$, of the peak corresponding to the internal standard in the chromatogram of the *Assay preparation A:*

$$S_{a(corr)} = S_{ha} - (S_i \times S_{ca} / S_{cb}),$$

in which S_{ha} and S_{ca} are the areas of the internal standard peak and the cetyl alcohol peak, respectively, in the chromatogram of the *Assay preparation A*.

Inject about 1 µL of each of the *Assay preparations C* and *D* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Carry out the correction for interference in the same manner as for the *Assay preparation A*, and calculate the corrected area, $S_{c(corr)}$, of the peak corresponding to the internal standard in the chromatogram of the *Assay preparation C*.

Procedure—Inject equal volumes of the *Resolution solution* and *Assay preparations C* and *D* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. The substances are eluted in the following order: cetyl alcohol, 1-heptadecanol (internal standard), and stearyl alcohol. Identify the cetyl alcohol and stearyl alcohol peaks in the chromatograms of the *Assay preparations*

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by comparison with the *Resolution solution*. Calculate the percentage of sodium cetyl sulfate in the portion of Sodium Cetostearyl Sulfate taken by the formula:

$$100A_c \times 1.421 \times W_{ch}(S_{c(corr)} \times W_c),$$

in which A_c is the area of the cetyl alcohol peak in the chromatogram of the *Assay preparation C;* W_{ch} is the weight of the internal standard, in mg, added in the preparation of the *Assay preparation C;* and W_c is the weight, in mg, of Sodium Cetostearyl Sulfate taken to prepare the *Assay preparation C*, calculated on the anhydrous basis.

Calculate the percentage of sodium stearyl sulfate in the portion of Sodium Cetostearyl Sulfate taken by the formula:

$$100\ B_c \times 1.377 \times W_{ch}/(S_{c(corr)} \times W_c),$$

in which B_c is the area of the stearyl alcohol peak in the chromatogram of the *Assay preparation C;* and the other terms are as defined above.■1S (*NF22*)

BRIEFING

Sorbitol, *NF 21* page 2841 and page 152 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Maltitol Solution*.

(EMC: C. Sheehan) RTS—39694-4

Change to read:

» Sorbitol contains not less than 91.0 percent and not more than 100.5 percent of ~~$C_6H_{14}O_6$,~~

■D-sorbitol,■1S (*NF22*)
calculated on the anhydrous basis. The amounts of

■total sugars,■1S (*NF22*)
other polyhydric alcohols, and any hexitol anhydrides, if detected, are not included in the requirements, nor

■in■1S (*NF22*)
the calculated amount under *Other Impurities.*

Change to read:
Packaging and storage~~— Preserve in tight containers.~~
■Preserve in well-closed containers. Store at room temperature.■1S (*NF22*)

Add the following:

■**Labeling**—Sorbitol intended for use in preparing parenteral dosage forms is so labeled.■1S (*NF22*)

Change to read:
USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■1S (*NF22*)
USP Sorbitol RS.

Add the following:

■**Microbial limits** ⟨61⟩—The total aerobic count using the *Plate Method* is not more than 10^3 cfu per g and the total combined molds and yeasts count is not more than 10^2 cfu per g.■1S (*NF22*)

Add the following:

■**pH** ⟨791⟩: between 3.5 and 7.0, in a 10% (w/w) solution in carbon dioxide-free water.■1S (*NF22*)

Change to read:
Water, *Method I* ⟨921⟩: not more than ~~1.0%.~~

■1.5%.■1S (*NF22*)

Change to read:
Residue on ignition ⟨281⟩: not more than 0.1%,

■determined on a 1.5-g portion, accurately weighed.■1S (*NF22*)

Delete the following:
■~~**Chloride** ⟨221⟩— A 1.5-g portion shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid (0.0050%).~~■1S (*NF22*)

Delete the following:
■~~**Sulfate** ⟨221⟩— A 1.0-g portion shows no more sulfate than corresponds to 0.10 mL of 0.020 N sulfuric acid (0.010%).~~■1S (*NF22*)

Delete the following:
■~~**Arsenic,** *Method II* ⟨211⟩: 3 ppm.~~■1S (*NF22*)

Delete the following:
■~~**Heavy metals** ⟨231⟩— Dissolve 2.0 g in 25 mL of water: the limit is 0.001%.~~■1S (*NF22*)

Change to read:
Reducing sugars~~— Transfer 7 g, accurately weighed, to a 400-mL beaker with the aid of 35 mL of water, and mix. Add 50 mL of alkaline cupric tartrate TS, cover the beaker, heat the mixture at~~

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~~such a rate that it comes to a boil in approximately 4 minutes, and boil for 2 minutes, accurately timed. Collect the precipitated cuprous oxide in a tared filtering crucible previously washed successively with hot water, with alcohol, and with ether and then dried at 105° for 30 minutes. Thoroughly wash the collected cuprous oxide on the filter with hot water, then with 10 mL of alcohol, and finally with 10 mL of ether, and dry at 105° for 30 minutes: the weight of the cuprous oxide does not exceed 50 mg. The amount determined in this test is not included in the calculated amount under *Other Impurities*.~~

■Dissolve 3.3 g of Sorbitol in 3 mL of water with the aid of gentle heat. ~~Proceed as directed in the test for *Reducing sugars* under *Mannitol* beginning with "Cool, and add 20.0 mL of cupric citrate TS".~~ Cool, and add 20.0 mL of cupric citrate TS and a few glass beads. Heat so that boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS using 2 mL of starch TS, added towards the end of the titration, as an indicator. Not less than 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to not more than 0.3% of reducing sugars, as glucose. The amount determined in this test is not included in the calculated amount under *Other Impurities*.■1S (*NF22*)

Delete the following:

■~~**Total sugars**—Place 2.1 g in a 250-mL flask fitted with a ground-glass joint, add 40 mL of approximately 0.1 N hydrochloric acid, attach a reflux condenser, and reflux for 4 hours. Transfer the solution to a 400-mL beaker, rinsing the flask with about 10 mL of water, neutralize with 6 N sodium hydroxide, and proceed as directed in the test for *Reducing sugars*, beginning with "Add 50 mL of alkaline cupric tartrate TS": the weight of the cuprous oxide does not exceed 50 mg. The amount determined in this test is not included in the calculated amount under *Other Impurities*.~~■1S (*NF22*)

Add the following:

■**Limit of nickel**—~~Proceed as directed in the test for *Nickel* under *Mannitol*. Not more than 1 µg per g is found.~~

Test solution—Dissolve 20.0 g of Sorbitol in diluted acetic acid, and dilute with diluted acetic acid to 150 mL. Add 2.0 mL of a saturated ammonium pyrrolidinedithiocarbamate solution (containing about 10 g of ammonium pyrrolidinedithiocarbamate per liter) and 10.0 mL of methyl isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer.

Blank solution—Prepare as directed for *Test solution*, except to omit the use of Sorbitol.

Standard solutions—Prepare as directed for *Test solution*, except to prepare three solutions by adding 0.5 mL, 1.0 mL, and 1.5 mL of nickel standard solution TS.

Procedure—Set the instrument to zero using the *Blank solution*. Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at least three times each, at the wavelength of maximum absorbance at 232.0 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a nickel hollow-cathode lamp and an air–acetylene flame. Record the average of the steady readings for each of the *Standard solutions* and the *Test solution*. Between each measurement, aspirate the *Blank solution*, and ascertain that the reading returns to zero. Plot the absorbances of the *Standard solutions* and the *Test solution* versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel in the *Test solution*. Not more than 1 µg per g is found.■1S (*NF22*)

Delete the following:

■~~**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements.~~■1S (*NF22*)

Add the following:

■**Other requirements**—If labeled for use in preparing parenteral dosage forms, it also meets the following requirements.

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Clarity and color of solution—Dissolve a 10.0-g portion in carbon dioxide-free water, and dilute with carbon dioxide-free water to 100.0 mL: the solution is clear and colorless.

Bacterial endotoxins ⟨85⟩: not more than 4 USP Endotoxin Units per g for parenteral dosage forms having a concentration of less than 100 g of sorbitol per liter and not more than 2.5 USP Endotoxin Units per g for parenteral dosage forms having a concentration of 100 g or more of sorbitol per liter.

Chloride ⟨221⟩—A 1.5-g portion shows no more chloride than corresponds to 0.10 mL of 0.020 N hydrochloric acid. Not more than 0.0050% is found.

Sulfate ⟨221⟩—A 1.0-g portion shows no more sulfate than corresponds to 0.10 mL of 0.020 N sulfuric acid. Not more than 0.01% is found. ■1S (*NF22*)

Change to read:

Assay—

Mobile phase—Use degassed water.

Resolution solution—Dissolve mannitol and USP Sorbitol RS in water to obtain a solution having concentrations of about 4.8 mg per ~~mL~~

■g ■1S (*NF22*)
of each.

Standard preparation—Dissolve an accurately weighed quantity of USP Sorbitol RS in water ~~, and dilute quantitatively with water~~

■ ■1S (*NF22*)
to obtain a solution having a known concentration of about 4.8 mg per ~~mL~~

■g. ■1S (*NF22*)

Assay preparation—~~Transfer about 0.24 g of Sorbitol, accurately weighed, to a 50-mL volumetric flask, dissolve in 10 mL of water, dilute with water to volume, and mix.~~

■Dissolve about 0.10 g of Sorbitol, accurately weighed, in water, and dilute with water to about 20 g. Accurately record the final solution weight, and mix thoroughly. ■1S (*NF22*)

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector that is maintained at a constant temperature ~~and a 7.8-mm × 30-cm column that contains packing L19. The column temperature is maintained at a temperature between 30° and 85°, controlled to within ± 2° of the selected temperature, and the flow rate is about 0.2 mL per minute.~~

■of about 35° and a 7.8-mm × 10-cm column that contains packing L34. The column temperature is maintained at a constant temperature of about 50°, controlled within ± 2°, and the flow rate is about 0.7 mL per minute. ■1S (*NF22*)
Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:*

■the relative retention times are about 0.6 for mannitol and 1.0 for sorbitol; and ■1S (*NF22*)
the resolution, *R*, between sorbitol and mannitol is not less than 2.0.

Procedure—Separately inject equal volumes ~~(about 20 µL)~~

■(about 10 µL) ■1S (*NF22*)
of the *Assay preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. ~~Calculate the quantity, in mg, of $C_6H_{14}O_6$, in the Sorbitol taken by the formula:~~

~~$$50C(r_U/r_S),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Sorbitol RS in the *Standard preparation*, and~~

■~~per mL, of~~ Calculate the percentage, on the anhydrous basis, of D-sorbitol in the portion of Sorbitol taken by the formula:

$$[10{,}000(C_S/C_U)(r_U/r_S)]/(100 - W),$$

in which C_S is the concentration, in mg per ~~mL,~~ g, of USP Sorbitol RS in the *Standard preparation;* C_U is the concentration, in mg per ~~mL,~~ g, of Sorbitol in the *Assay preparation;* ■1S (*NF22*)
r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively;

■and W is the percentage obtained in the test for *Water*. ■1S (*NF22*)

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BRIEFING

Anhydrized Liquid Sorbitol, page 154 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Maltitol Solution*.

(EMC: C. Sheehan) RTS—39694-5

Add the following:

■Anhydrized Liquid Sorbitol

» Anhydrized Liquid Sorbitol is a water solution containing, on the anhydrous basis, not less than 25.0 percent of D-sorbitol ($C_6H_{14}O_6$) and not less than 15.0 percent of 1,4-sorbitan ($C_6H_{12}O_5$). The amounts of total sugars, other polyhydric alcohols, and any other hexitol anhydrides, if detected, are not included in the requirements or in the calculated amount under *Other Impurities*.

Packaging and storage—~~Preserve in tight containers.~~ Preserve in well-closed containers. Do not store below 20°.

Labeling—The labeling indicates the percentage content, on the anhydrous basis, of D-sorbitol and 1,4-sorbitan.

USP Reference standards ⟨11⟩—*USP Sorbitol RS. USP 1,4-Sorbitan RS.*

Identification—

A: Dissolve 1.4 g of Anhydrized Liquid Sorbitol in 75 mL of water. Transfer 3 mL of this solution to a 15-cm test tube, add 3 mL of freshly prepared catechol solution (1 in 10), and mix. Add 6 mL of sulfuric acid, mix again, then gently heat the tube in a flame for about 30 seconds: a deep pink or wine-red color appears.

B: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

Microbial limits ⟨61⟩—The total aerobic microbial count using the *Plate Method* is not more than 10^3 cfu per mL. The total combined molds and yeasts count is not more than 10^2 cfu per mL.

pH ⟨791⟩: between 4.0 and 7.0, in a 14% (w/w) solution of Anhydrized Liquid Sorbitol in carbon dioxide-free water.

Water, *Method I* ⟨921⟩: not more than 31.5%.

Residue on ignition ⟨281⟩: not more than 0.20%, calculated on the anhydrous basis. Determine on a 2-g portion, accurately weighed.

Reducing sugars—To an amount of Anhydrized Liquid Sorbitol, equivalent to 3.3 g, on the anhydrous basis, add 3 mL of water, 20.0 mL of cupric citrate TS, and a few glass beads. ~~Proceed as directed in the test for *Reducing sugars* under *Mannitol*, beginning with "Heat so that boiling begins."~~ Heat so that boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS using 2 mL of starch TS, added towards the end of the titration, as an indicator. Not less than 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to not more than 0.3% of reducing sugars, on the anhydrous basis, as glucose. The amount determined in this test is not included in the calculated amount under *Other Impurities*.

Limit of nickel—

Test solution—Dissolve 20.0 g of Anhydrized Liquid Sorbitol in diluted acetic acid, and dilute with diluted acetic acid to 100.0 mL. Add 2.0 mL of a saturated solution of ammonium pyrrolidine dithiocarbamate (about 10 g of ammonium pyrrolidine dithiocarbamate per liter) and 10.0 mL of methyl

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isobutyl ketone, and shake for 30 seconds. Protect from bright light. Allow the two layers to separate, and use the methyl isobutyl ketone layer.

Blank solution—Prepare as directed for the *Test solution*, except to omit the use of Anhydrized Liquid Sorbitol. Quantities should be increased five fold to ensure that a sufficient volume of *Blank solution* is available.

Standard solutions—Prepare as directed for the *Test solution*, except to prepare three solutions by adding 0.5 mL, 1.0 mL, and 1.5 mL of nickel standard solution TS.

Procedure— ~~Proceed as directed in the test for *Nickel* under *Mannitol*.~~ Set the instrument to zero using the *Blank solution*. Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at least three times each, at the wavelength of maximum absorbance at 232.0 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a nickel hollow-cathode lamp and an air–acetylene flame. Record the average of the steady readings for each of the *Standard solutions* and the *Test solution*. Between each measurement, aspirate the *Blank solution*, and ascertain that the reading returns to zero. Plot the absorbances of the *Standard solutions* and the *Test solution* versus the added quantity of nickel. Extrapolate the line joining the points on the graph until it meets the concentration axis. The distance between this point and the intersection of the axes represents the concentration of nickel in the *Test solution*. Not more than 1 µg per g, calculated on the anhydrous basis, is found.

Assay—

Mobile phase—Use degassed water.

Resolution solution—Dissolve sorbitol, 1,4-sorbitan, isosorbide, and mannitol in water to obtain a solution having concentrations of about 10 mg per g, 4 mg per g, 4 mg per g, and 1 mg per g, respectively.

Standard preparation—Dissolve accurately weighed quantities of USP Sorbitol RS and USP 1,4-Sorbitan RS in water to obtain a solution having concentrations of about 10 mg per g and 4 mg per g, respectively.

Assay preparation—Dissolve about 0.40 g of Anhydrized Liquid Sorbitol, accurately weighed, in water, and dilute with water to about 20 g. Accurately record the final solution weight, and mix thoroughly.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector that is maintained at a constant temperature of about 35°, and a 7.8-mm × 10-cm column that contains packing L34. The column temperature is maintained at about 50°, controlled within ± 2°, and the flow rate is about 0.6 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the resolution, *R*, between the 1,4-sorbitan and isosorbide is not less than 2.0. Chromatograph the *Standard preparation*, and record the peak responses for 1,4-sorbitan and sorbitol as directed for *Procedure:* the relative retention times are about 0.35 for 1,4-sorbitan, 0.43 for isosorbide, 0.7 for mannitol, and 1.0 for sorbitol; and the relative standard deviation for replicate injections is not more than 2.0% for each analyte.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Separately calculate the percentages, on the anhydrous basis, of 1,4-sorbitan and sorbitol in the portion of Anhydrized Liquid Sorbitol taken by the formula:

$$[10{,}000(C_S / C_U)(r_U / r_S)]/(100 - W),$$

in which C_S is the concentration, in mg per g, of the appropriate USP Reference Standard in the *Standard preparation;* C_U is the concentration, in mg per g, of the Anhydrized Liquid Sorbitol in the *Assay preparation;* r_U and r_S are the peak

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responses of the corresponding analyte obtained from the *Assay preparation* and the *Standard preparation*, respectively; and *W* is the percentage obtained in the test for *Water*.■1S (*NF22*)

BRIEFING

Noncrystallizing Sorbitol Solution, *NF 21* page 2842 and page 156 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Maltitol Solution*.

(EMC: C. Sheehan) RTS—39694-2

Change to read:

» Noncrystallizing Sorbitol Solution is an aqueous solution ~~of hydrogenated, fully and partially hydrolyzed starches. It contains~~

▲containing▲*NF22*
not less than 45.0 percent of D-sorbitol ($C_6H_{14}O_6$) (w/w). The amounts of total sugars, other polyhydric alcohols, and any hexitol anhydrides, if detected, are not included in the requirements nor

▲in▲*NF22*
the calculated amount under *Other Impurities*.

Change to read:

Packaging and storage— ~~Preserve in tight containers.~~

▲Preserve in well-closed containers. Do not store below 20°.▲*NF22*

Change to read:

Identification—

A: ~~To 3 mL of a 1 in 75 dilution of it in~~

▲Dissolve 1.4 g of Noncrystallizing Sorbitol Solution in 75 mL of water. Transfer 3 mL of this solution to▲*NF22*
a 15-cm test tube, add 3 mL of freshly prepared catechol solution (1 in 10), mix, add 6 mL of sulfuric acid, mix again, and gently heat the tube in a flame for about 30 seconds: a deep pink or wine-red color appears.

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

Delete the following:

▲~~**Specific gravity** ⟨841⟩: not less than 1.290.~~▲*NF22*

Delete the following:

▲~~**Refractive index** ⟨831⟩: between 1.457 and 1.467.~~▲*NF22*

Add the following:

▲**Microbial limits** ⟨61⟩—The total aerobic microbial count using the *Plate Method* is not more than 10^3 cfu per mL, and the total combined molds and yeasts count is not more than 10^2 cfu per mL.▲*NF22*

Add the following:

▲**pH** ⟨791⟩: between 5.0 and 7.5, in a 14% (w/w) solution of Noncrystallizing Sorbitol Solution in carbon dioxide-free water.▲*NF22*

Add the following:

▲**Water,** *Method I* ⟨921⟩: between 28.5% and 31.5%.▲*NF22*

Add the following:

▲**Residue on ignition** ⟨281⟩: not more than 0.1%, calculated on the anhydrous basis, determined on a 2-g portion, accurately weighed.▲*NF22*

Delete the following:

▲~~**Heavy metals,** *Method I* ⟨231⟩: 0.001%.~~▲*NF22*

Change to read:

Reducing sugars—

~~*Cupric sulfate-iodide solution*— Dissolve 81 g of potassium citrate monohydrate, 92 g of potassium oxalate, and 74 g of potassium carbonate in hot water, and dilute with water to 600 mL (*Solution A*). Dissolve 25 g of cupric sulfate in hot water, and dilute with water to 200 mL. Combine this solution with *Solution A*, and mix for 30 minutes (*Solution B*). Dissolve 0.4 g of sodium hydroxide in about 100 mL of water. Dissolve 3.4 g of potassium iodate and 50 g of potassium iodide in this sodium hydroxide solution, and dilute with water to 200 mL (*Solution C*). Add *Solution C* to *Solution B*, and stir for at least 2 hours.~~

~~*Procedure*— Transfer about 30 g of Solution, accurately weighed, to a 300-mL conical flask. Adjust the volume of the solution with water to 50 mL, and add 50.0 mL of *Cupric sulfate-iodide solution*. Connect a suitable condenser to the flask, heat on a hot plate adjusted to bring the solution to a boil within 3 minutes, and gently reflux the solution for 5 minutes. Remove the flask from the hot plate, and cool it in a water bath at 20° for 15 to 25 minutes. Do not overcool. Slowly add 25 mL of 5 N sulfuric acid, and swirl gently to mix. [NOTE— Foaming may occur when the 5 N sulfuric acid is added.] Titrate the liberated iodine with 0.1 N sodium thiosulfate VS to a pale green color. Add 1 mL of starch TS, mix, and continue the titration to a pale green-blue endpoint. Perform a blank determination (see *Titrimetry* ⟨541⟩), and make any necessary correction. Calculate the titration difference, based on a 30-g specimen weight, by the formula:~~

~~$(30 / W)(0.1 / N)(B - S)$,~~

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~~in which *W* is the weight, in g, of the Solution taken, N is the normality of the sodium thiosulfate VS, and *B* and *S* are the volumes, in mL, of sodium thiosulfate consumed in the blank and specimen titrations, respectively. The titration difference is not more than 21.1 mL, corresponding to 0.21% reducing sugars (as dextrose). The amount determined in this test is not included in the calculated amount under *Other Impurities*.~~

■To an amount of Noncrystallizing Sorbitol Solution, equivalent to 3.3 g on the anhydrous basis, add 3 mL of water, 20.0 mL of cupric citrate TS, and a few glass beads. ~~Proceed as directed in the test for *Reducing sugars* under *Mannitol*, beginning with "Heat so that boiling begins."~~ Heat so that boiling begins after 4 minutes, and maintain boiling for 3 minutes. Cool rapidly, and add 40 mL of diluted acetic acid, 60 mL of water, and 20.0 mL of 0.05 N iodine VS. With continuous shaking, add 25 mL of a mixture of 6 mL of hydrochloric acid and 94 mL of water. When the precipitate has dissolved, titrate the excess of iodine with 0.05 N sodium thiosulfate VS using 2 mL of starch TS, added towards the end of the titration, as an indicator. Not less than 12.8 mL of 0.05 N sodium thiosulfate VS is required, corresponding to not more than 0.3% of reducing sugars, on the anhydrous basis, as glucose. The amount determined in this test is not included in the calculated amount under *Other Impurities*.■1S (*NF22*)

Add the following:

■**Limit of nickel**—Proceed as directed in the test for *Limit of nickel* under *Sorbitol Solution.* Not more than 1 µg per g, calculated on the anhydrous basis, is found.■1S (*NF22*)

Delete the following:

~~▲**Other requirements**—It meets the requirements for *Water*, *Residue on ignition*, *Chloride*, *Sulfate*, and *Arsenic*, under *Sorbitol Solution, USP*.▲*NF22*~~

Change to read:

Assay—

~~*Mobile phase*—Use filtered and degassed water.~~

~~*Standard preparation*—Transfer an accurately weighed quantity of about 30 mg of USP Sorbitol RS to a 1 mL volumetric flask, dissolve in and dilute with water to volume, and mix.~~

~~*Assay preparation*—Transfer about 2.0 g of Solution, accurately weighed, to a 50 mL volumetric flask, dilute with water to volume, and mix.~~

~~*Resolution solution*—Dissolve 1.5 mg of mannitol in 0.5 mL of the *Standard preparation*, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector maintained at 25°, a 4.6 mm × 3 cm guard column containing packing L34, and a 7.8 mm × 10 cm analytical column containing packing L34 and maintained at 85°. The flow rate is about 0.6 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed under *Procedure*: the relative retention times are about 0.7 for mannitol and 1.0 for sorbitol, and the resolution, *R*, between the mannitol peak and the sorbitol peak is not less than 2.0. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_6H_{14}O_6$ in the portion of Solution taken by the formula:~~

$$~~50C(r_U/r_S),~~$$

~~in which *C* is the concentration, in mg per mL, of USP Sorbitol RS in the *Standard preparation*, and r_U and r_S are the Sorbitol peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

▲*Mobile phase*, *Resolution solution*, *Standard preparation*, and *Chromatographic system*—Proceed as directed in the *Assay* under *Sorbitol.*

Assay preparation—Accurately weigh about 0.20 g of Noncrystallizing Sorbitol Solution, dissolve in and dilute with water to about 20 g. Accurately record the final solution weight, and mix thoroughly.

Procedure—Proceed as directed in the *Assay* under *Sorbitol*. Calculate the percentage of D-sorbitol ($C_6H_{14}O_6$) in the portion of Noncrystallizing Sorbitol Solution taken by the formula:

$$100(C_S/C_U)(r_U/r_S),$$

in which C_S is the concentration, in mg per g, of USP Sorbitol RS in the *Standard preparation;*~~, calculated on the anhydrous basis;~~ C_U is the concentration, in mg per g, of Noncrystallizing Sorbitol Solution in the *Assay preparation;*~~, calculated on the anhydrous basis;~~ and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.▲*NF22*

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BRIEFING

Modified Starch, page 1221 of *PF* 28(4) [July–Aug. 2002]; **Pregelatinized Modified Starch,** page 1222 of *PF* 28(4) [July–Aug. 2002]. On the basis of comments received, these new monographs are being presented again with additional changes. It is proposed to include treatment with enzymes in the Definition for *Modified Starch*. It is proposed to include *Wheat starch* and *Potato starch* under *Botanic characteristics* as sources of Modified Starches. It is proposed to replace the existing *Identification* test *A* because it was found that some modified starch products gave results outside the criteria for this test and to modify *Identification* test *B* to be consistent with proposed changes to the draft harmonization *Corn Starch* monograph. Under the test for *Microbial limits*, it is proposed to include tests for both total microbial count and total combined molds and yeasts in order to achieve consistency with monographs of similar articles. It is also proposed to make the pH range consistent with Food Chemical Codex specifications for Food Starch, modified, and to use the test for *Oxidizing substances* from the current *Starch* monograph rather than from the current *Pregelatinized Starch* monograph.

(EMC: C. Sheehan; AMB: D. Porter) RTS—39959-1

Add the following:

■Modified Starch

» Modified Starch is Starch modified by chemical means. Food Starch may be acid-modified, bleached, oxidized, esterified, ~~or~~ etherified, or treated enzymatically to change the functional properties (21 CFR 172.892).

Packaging and storage—~~Preserve~~ Store in well-closed containers at temperatures ranging from 0° to 55°.

Botanic characteristics—

Corn starch—Polygonal, rounded or spheroidal granules up to about 35 µm in diameter and usually having a circular or several-rayed central cleft.

Tapioca starch—Spherical granules with one truncated side, typically 5 to 35 µm in diameter and usually having a circular or several-rayed central cleft.

Potato starch—Irregularly shaped, ovoid, or pear-shaped granules, usually 30 to 100 µm in size but occasionally exceeding 100 µm; or rounded, 10 to 35 µm in size. There are occasional compound granules having two to four components. The ovoid and pear-shaped granules have an eccentric hilum, and the rounded granules have accentric or slightly eccentric hilum. All granules show clearly visible concentric striations.

Wheat starch—Large and small granules, usually 10 to 60 µm in diameter. The central hilum and striations are visible or barely visible.

Identification—

A: ~~Prepare a smooth mixture of 1 g of Modified Starch with 2 mL of cold water, stir into 15 mL of boiling water, boil gently for 2 minutes, and cool to room temperature: the product is translucent to clear.~~ Prepare a 2% (w/w) sodium hydroxide solution. Weigh 0.6 g of Modified Starch, and transfer to a 25-mL glass vial with a plastic cap. Add 9.4 g of water, cap, and shake vigorously to evenly disperse the starch. Add 10 g of 2% NaOH solution, cap, and shake vigorously for 1 minute to create a smooth mixture. Evaluate within 1 minute. The final solution is translucent to opaque with a fluid consistency. A yellow tint of the final solution is acceptable.

B: A water slurry of the Modified Starch is colored ~~reddish violet~~ orange-red to deep blue by iodine TS.

Microbial limits ⟨61⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic microbial count does not exceed 10^3 cfu per g; the total combined molds and yeasts count does not exceed 10^2 cfu per g.

pH ⟨791⟩—Weigh 20.0 ± 0.1 g of Modified Starch, transfer to a suitable nonmetallic container, and add 100 mL of water to obtain a slurry. Stir using a magnetic stirrer at a moderate rate for about 5 minutes, and determine the pH to the nearest 0.1 unit: between ~~4.5 and 8.0.~~ 3.0 and 9.0.

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Loss on drying ⟨731⟩—Dry it at 120° for 4 hours. ~~it loses not more than 14% of its weight.~~ *Corn starch*, *Wheat starch*, and *Tapioca starch:* not more than 15.0%; *Potato starch:* not more than 21.0%.

Residue on ignition ⟨281⟩: not more than 0.5%, a test specimen of 2.0 ± 0.1 g being used.

Iron ⟨241⟩: 0.002%, the *Test Preparation* being prepared as follows. Dissolve the residue obtained in the test for *Residue on ignition* in 8 mL of hydrochloric acid with the aid of gentle heating. Dilute with water to 100 mL in a volumetric flask, and mix. Dilute 25 mL of this solution with water to 47 ± 1 mL.

Oxidizing substances ~~To 5 g of Modified Starch add 20 mL of a mixture of methanol and water (1:1), then add 1 mL of 6 N acetic acid, and stir until a homogeneous suspension is obtained. Add 0.5 mL of a freshly prepared saturated solution of potassium iodide, mix, and allow to stand for 5 minutes: no distinct blue, brown, or purple color is observed.~~ Transfer 4.0 g to a glass-stoppered, 125-mL conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Transfer to a glass-stoppered, 50-mL centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, 125-mL conical flask. Add 1 mL of glacial acetic acid and 0.5 g to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodine color. Perform a blank determination, and make any necessary correction. Each mL of 0.002 N sodium thiosulfate is equivalent to 34 µg of oxidant, calculated as hydrogen peroxide. Not more than 12.6 mL of 0.002 N sodium thiosulfate is required (180 µg per g, calculated as H_2O_2): not more than 0.018% of oxidizing substances is found.

Limit of sulfur dioxide—Mix 20.0 ± 0.1 g of Modified Starch with 200 mL of 5 percent alcohol until a smooth suspension is obtained, and vacuum filter through paper (Whatman No.1 or equivalent). To 100 mL of the filtrate add 3 mL of starch TS, and titrate with 0.10 N iodine to the first permanent blue color. Not more than 2.7 mL is consumed: not more than ~~0.008%~~ 0.005% of sulfur dioxide is found. ■1S (*NF22*)

BRIEFING

Pregelatinized Modified Starch, page 1222 of *PF* 28(4) [July–Aug. 2002]—See briefing under *Modified Starch*.

(EMC: C. Sheehan; AMB: D. Porter) RTS—39960-1

Add the following:

■Pregelatinized Modified Starch

» Pregelatinized Modified Starch is Modified Starch that has been chemically or mechanically processed, or both, to rupture all or part of the granules to produce a product that swells in cold water.

Identification—

A: ~~Prepare a smooth mixture of 1 g of Pregelatinized Modified Starch with 2 mL of cold water, stir into 15 mL of boiling water, boil gently for 2 minutes, and cool to room temperature: the product is translucent to clear.~~ Prepare a 2% (w/w) sodium hydroxide solution. Weigh 0.6 g of Pregelatinized Modified Starch, and transfer to a 25-mL glass vial with a plastic cap. Add 9.4 g of water, cap, and shake vig-

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orously to evenly disperse the starch. Add 10 g of 2% NaOH solution, cap, and shake vigorously for 1 minute to create a smooth mixture. Evaluate within 1 minute. The final solution is translucent to opaque with a fluid consistency. A yellow tint of the final solution is acceptable.

B: An aqueous dispersion of Pregelatinized Modified Starch is colored ~~reddish violet~~ orange-red to deep blue by iodine TS.

pH ⟨791⟩—Wet 10.0 ± 0.1 g of Pregelatinized Modified Starch with 10 mL of alcohol, then dilute with water to 300 mL to obtain an aqueous dispersion. Stir continuously at a moderate rate for 5 minutes, and determine the pH to the nearest 0.1 unit: between ~~4.5 and 8.0.~~ 3.0 and 9.0.

Loss on drying ⟨731⟩—Dry it at 120° for 4 hours: it loses not more than 15% of its weight.

Residue on ignition ⟨281⟩: not more than 1.5%, a test specimen of 2.0 ± 0.1 g being used.

Oxidizing substances—To 5 g of Pregelatinized Modified Starch add 20 mL of a mixture of methanol and water (1:1), then add 1 mL of 6 N acetic acid, and stir until a homogeneous suspension is obtained. Add 0.5 mL of a freshly prepared saturated solution of potassium iodide, mix, and allow to stand for 5 minutes: no distinct blue, brown, or purple color is observed.

Limit of sulfur dioxide—Mix 20.0 ± 0.1 g of Pregelatinized Modified Starch with 100 mL of 95 percent alcohol, and stir for several minutes to completely wet the starch. Slowly add 100 mL of water, and stir until a smooth suspension is obtained. Allow the starch mixture to set undisturbed until most of the starch has settled, and filter the aqueous portion through paper (Whatman No. 1 or equivalent). To 100 mL of the clear filtrate add 100 mL of water, and mix. Add 3 mL of starch TS, and titrate with 0.010 N iodine to the first permanent blue or purple color. Not more than 2.7 mL is consumed: not more than ~~0.008%~~ 0.005% of sulfur dioxide is found.

Other requirements—It meets the requirements for *Packaging and storage* and in the tests for *Microbial limits* ~~*, Loss on drying*~~, and *Iron*~~, and *Oxidizing substances*~~ under *Modified Starch*. ■1S (*NF22*)

BRIEFING

Tapioca Starch, page 838 of *PF* 28(3) [May–June 2002]. This new monograph is being presented again with a proposed change to the *Packaging and storage* section, to incorporate specifications provided by the manufacturer. A new volumetric solution is also proposed for use in the test for *Limit of sulfur dioxide*.

(EMC: C. Sheehan; PSD: C. Okeke) RTS—39936-1

Add the following:

▲Tapioca Starch

» Tapioca Starch consists of the starch granules separated from the tubers of tapioca (cassava) [*Manihot utilissima* Pohl (Fam. Euphorbiaceae)].

Change to read:

Packaging and storage—Preserve in well-closed containers. ■Store at 25°, excursion permitted up to 40°.■1S (*NF22*)

Botanic characteristics—Examine Tapioca Starch under a microscope, using not less than 20× magnification and using glycerin as the mounting agent: it appears as spherical granules with one truncated side, typically having a 5- to 35-µm diameter and having circular or several-rayed central clefts.

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Identification—

A: Suspend 1 g of Tapioca Starch in 50 mL of water, boil for 1 minute, and cool: a thin, cloudy mucilage is formed.

B: To 10 mL of the mucilage obtained in *Identification* test *A* add 0.04 mL each of iodine and potassium iodide TS: a reddish violet to dark blue color is produced, which disappears on heating and reappears on cooling.

Microbial limits ⟨61⟩—It meets the requirements of the test for absence of *Escherichia coli.* The total aerobic microbial count does not exceed 10^3 cfu per g, and the total combined molds and yeasts count does not exceed 10^2 cfu per g.

pH ⟨791⟩—Weigh 20.0 ± 0.1 g of Tapioca Starch, transfer to a suitable nonmetallic container, and add 100 mL of water to obtain a slurry. Agitate continuously at a moderate rate for 5 minutes, then stop agitation, and immediately determine the pH: between 4.5 and 7.0.

Loss on drying ⟨731⟩—Dry it at 130° for 90 minutes: it loses not more than 16.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.6%, determined on a 1.0-g specimen.

Iron ⟨241⟩: 0.002%, the *Test Preparation* being prepared as follows. Shake ~~0.75 g~~ 0.25 g of Tapioca Starch with 15 mL of 0.1 N hydrochloric acid, and filter. Use 10 mL of this solution as the *Test Preparation.*

Limit of oxidizing substances—Transfer 4.0 g of Tapioca Starch to a glass-stoppered, 125-mL conical flask, and add 50.0 mL of water. Insert the stopper, and swirl for 5 minutes. Decant into a glass-stoppered, 50-mL centrifuge tube, and centrifuge to clarify. Transfer 30.0 mL of the clear supernatant to a glass-stoppered, 125-mL conical flask. Add 1 mL of glacial acetic acid and 0.5 to 1.0 g of potassium iodide. Insert the stopper, swirl, and allow to stand for 25 to 30 minutes in the dark. Add 1 mL of starch TS, and titrate with 0.002 N sodium thiosulfate VS to the disappearance of the starch-iodide color. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.002 N sodium thiosulfate is equivalent to 34 µg of oxidant, calculated as hydrogen peroxide. Not more than 1.4 mL of 0.002 N sodium thiosulfate is required: not more than 0.002% of oxidizing substances is found.

Change to read:

Limit of sulfur dioxide—Mix 20 g of Tapioca Starch with 200 mL of water until a smooth suspension is obtained, and filter. To 100 mL of the clear filtrate add 3 mL of starch TS, and titrate with ~~0.010 N~~ ■0.01 $N_{■1S\ (NF22)}$ iodine solution ■$VS_{■1S\ (NF22)}$ to the first permanent blue color. Not more than 1.7 mL is consumed: not more than 0.005% of sulfur dioxide is found.▲*NF22*

BRIEFING

Stearoyl Macrogolglycerides, page 1223 of *PF* 28(4) [July–Aug. 2002]. This proposed new monograph is being presented again with changes approved by the Expert Committee on Nomenclature and Labeling. The changes reflect terminology used in the United States, particularly in several excipient standards appearing in the *National Formulary.* The term "polyethylene glycol" and the "polyoxyl" designations for esters and ethers formed with polyethylene glycol and organic acids and alcohols or polyols replace the "macrogol" terminology that is seen elsewhere.

(EMC: C. Sheehan; NL: C. Barnstein) RTS—39930-1

Add the following:

■Stearoyl ~~Macrogolglycerides~~ Polyoxylglycerides

» Stearoyl ~~Macrogolglycerides~~ Polyoxylglycerides are mixtures of monoesters, diesters, and triesters of glycerol and monoesters and diesters of ~~macrogols~~ polyethylene glycols with a nominal

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mean relative molecular weight between 300 and 4000. They are produced by partial alcoholysis of saturated oils, mainly containing triglycerides of stearic acid, with ~~macrogol,~~ polyethylene glycol, by esterification of glycerol and ~~macrogol~~ polyethylene glycol with fatty acids, or as a mixture of glycerol esters and ethylene oxide condensate with the fatty acids of the hydrogenated oils. The Hydroxyl Value does not differ by more than 15 units from the nominal value, and the Saponification Value does not differ by more than 10 units from the nominal value. The average molecular weight is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value.

Packaging and storage—Preserve in tight containers, protected from light and moisture. Store at controlled room temperature.

Labeling—Label it to indicate the average nominal molecular weight of esters as part of the official title. The label also indicates the Hydroxyl Value and the Saponification Value.

USP Reference standards ⟨11⟩—*USP Stearoyl ~~Macrogol-glycerides~~ Polyoxylglycerides RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements for *Identification* test *B* under *Caprylocaproyl ~~Macrogolglycerides.~~ Polyoxylglycerides.*

Acid value ⟨401⟩: not more than 2.0, determined on a 2.0-g specimen.

Hydroxyl value ⟨401⟩—The Hydroxyl Value, between 25 and 56, does not differ by more than 15 units from the nominal value, determined on a 1.0-g specimen, accurately weighed.

Iodine value ⟨401⟩: not more than 2.0.

Peroxide value ⟨401⟩: not more than 6.0, determined on a 2.0-g specimen.

Saponification value ⟨401⟩—The Saponification Value, between 67 and 112, does not differ by more than 10 units from the nominal value, determined on a 2.0-g specimen.

Fatty acid composition ⟨401⟩: not more than 5.0% each of lauric acid and myristic acid is found; between 40.0% and 50.0% of palmitic acid is found; and between 48.0% and 58.0% of stearic acid is found.

Water, *Method I* ⟨921⟩: not more than 1.0%, determined on a 1.0-g specimen.

Total ash ⟨561⟩: not more than 0.2%, determined on a 1.0-g specimen.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Limit of free ethylene oxide and dioxane—Proceed as directed in the test for *Limit of free ethylene oxide and dioxane* under *Caprylocaproyl ~~Macrogolglycerides~~ Polyoxylglycerides:* not more than 1 µg of ethylene oxide per g is found; and not more than 10 µg of dioxane per g is found.

Limit of free glycerol—Proceed as directed in the test for *Limit of free glycerol* under *Caprylocaproyl ~~Macrogolglycerides~~ Polyoxylglycerides:* not more than 5.0% is found.■1S (*NF22*)

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GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

〈**11**〉 **Reference Standards,** *USP 26* page 1966, page 3005 of the *First Supplement,* page 3212 of *PF* 22(6) [Nov.–Dec. 1996], page 4500 of *PF* 23(4) [July–Aug. 1997], page 5180 of *PF* 23(6) [Nov.–Dec. 1997], page 6925 of *PF* 24(5) [Aug.–Sept. 1998], page 8222 of *PF* 25(3) [May–June 1999], page 8561 of *PF* 25(4) [July–Aug. 1999], page 8893 of *PF* 25(5) [Sept.–Oct. 1999], page 9222 of *PF* 25(6) [Nov.–Dec. 1999], page 218 of *PF* 26(1) [Jan.–Feb. 2000], page 471 of *PF* 26(2) [Mar.–Apr. 2000], page 793 of *PF* 26(3) [May–June 2000], page 1101 of *PF* 26(4) [July–Aug. 2000], page 1369 of *PF* 26(5) [Sept.–Oct. 2000], page 1606 of *PF* 26(6) [Nov.–Dec. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 2268 of *PF* 27(2) [Mar.–Apr. 2001], page 2594 of *PF* 27(3) [May–June 2001], page 2806 of *PF* 27(4) [July–Aug. 2001], page 3071 of *PF* 27(5) [Sept.–Oct. 2001], page 3348 of *PF* 27(6) [Nov.–Dec. 2001], page 111 of *PF* 28(1) [Jan.–Feb. 2002], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 839 of *PF* 28(3) [May–June 2002], page 1224 of *PF* 28(4) [July–Aug. 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 1913 of *PF* 28(6) [Nov.–Dec. 2002], page 163 of *PF* 29(1) [Jan.–Feb. 2003], page 483 of *PF* 29(2) [Mar.–Apr. 2003], and page 710 of *PF* 29(3) [May–June 2003].

(HDQ) RTS—38539-2; 39761-1; 39773-1; 39859-1; 39884-1; 39894-1; 39894-4; 39903-4; 39903-5; 39917-1; 39918-3; 39918-4; 39918-5; 39930-1

Add the following:

■**USP Betahistine Hydrochloride RS—**Dry portion at 100° to 105° to constant weight before using.■1S (*USP27*)

Change to read:
USP Brinzolamide Related Compound B RS ~~[desethyl brinzolamide oxalate]~~ ■[(*R*-4-amino)-2,3-dihydro-2-(3-methoxypropyl)-4*H*-thieno[3,2,-*e*]-thiazine-6-sulfonamide-1,1-dioxide ethandioate 1:1]■1S (*USP27*)
($C_{10}H_{17}N_3O_5S_3 \cdot C_2H_2O_4$ ✧ 445.49)—Do not dry.

Delete the following:
■~~**USP Cinoxate RS.**~~■1S (*USP27*)

Add the following:

■**USP Cyclandelate RS**—Dry portion over silica gel for 24 hours before using.■1S (*USP27*)

Add the following:

■**USP Gamma Cyclodextrin RS—**[To come.]■1S (*USP27*)

Add the following:

■**USP Gemcitabine Hydrochloride RS**—Do not dry before using. Preserve in well-closed containers.■1S (*USP27*)

Add the following:

■**USP Irbesartan RS**—Do not dry.■1S (*USP27*)

Add the following:

■**USP Loratadine RS.**■1S (*USP27*)

Delete the following:
■~~**USP Mandelic Acid RS**—Do not dry. Determine the water content titrimetrically at the time of use. Keep container tightly closed and protected from light.~~■1S (*USP27*)

Add the following:

■**USP Nimodipine RS.**■1S (*USP27*)

Add the following:

■**USP Nimodipine Related Compound A RS** [Bis(2-methoxyethyl) 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate] ($C_{21}H_{23}N_2O_7$ ✧ 415.14).■1S (*USP27*)

Add the following:

■**USP Polyoxyl Lauryl Ether RS.**■1S (*USP27*)

Add the following:

■**USP Polyoxyl Oleate RS.**■1S (*USP27*)

Add the following:

■**USP Polyoxyl Stearyl Ether RS.**■1S (*USP27*)

Add the following:

■**USP Quinapril Hydrochloride RS**—Do not dry.■1S (*USP27*)

Add the following:

■**USP Quinapril Related Compound A RS** [Ethyl [3*S*-[2*R**), 3a, 11ab]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-a-(2-phenylethyl)-2*H*-pyrazino[1,2, b]isoquinoline-2-acetate] ($C_{25}H_{27}N_2O_4$ ✧ 419.49)—Do not dry.■1S (*USP27*)

Add the following:

■**USP Quinapril Related Compound B RS** [3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3*S*-[2[*R**(*R**)], 3*R**]] ($C_{23}H_{26}N_2O_5$ ✧ 410.47)—Do not dry.■1S (*USP27*)

Add the following:

■**USP Stearoyl ~~Macrogolglycerides~~ Polyoxylglycerides RS**—Store in original container and prevent exposure to air, heat, and moisture.■1S (*USP27*)

BRIEFING

⟨**311**⟩ **Alginates Assay,** *USP 26* page 2062 and page 643 of *PF* 26(3) [May–June 2000]. The modified general test chapter *Alginates Assay* ⟨311⟩, which previously appeared in *Pharmacopeial Previews*, is now forwarded, with changes, to *In-Process Revision*. It is proposed to revise the *System Suitability* section to address comments received regarding the blank determination and the determination of percentage carbon dioxide released from the standard. For clarification purposes, a formula for calculating the blank determination has been added and limits for percentage carbon dioxide released from the standard have also been added.

(EMC: D. Bempong) RTS—39912-1

Delete the following:

■~~In a suitable closed system, liberate the carbon dioxide from the uronic acid groups of about 250 mg of the test specimen by heating with about 6 N hydrochloric acid, and sweep the carbon dioxide by means of an inert gas into a titration vessel containing25.0 mL of 0.25 N sodium hydroxide VS. Add 10 mL of barium chloride solution (1 in 10) to the titration vessel, insert a tight stopper, and shake the flask gently for 1 to 2 minutes. Allow to stand for at least 5 minutes. Add 3 drops of phenolphthalein TS, and titrate with 0.1 N hydrochloric acid VS to the first loss of a pink endpoint. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 0.25 N sodium hydroxide consumed is equivalent to 5.5 mg of carbon dioxide (CO_2).~~

~~In a suitable system, precautions must be taken against leakage and overheating of the reaction mixture, and there should be adequate sweeping time and avoidance of entrainment of hydrochloric acid. The system is not considered to be suitable unless a 250-mg test specimen of D-glucuronolactone, accurately weighed, results in a net titration value between 11.0 and 11.7 mL of 0.25 N sodium hydroxide. One suitable system, with accompanying procedure, is given below.~~■1S (*USP27*)

Delete the following:

■~~APPARATUS~~

~~The apparatus shown in the accompanying diagram consists essentially of a soda-lime column, *A*, a mercury valve, *B*, connected through a side arm to a reaction flask, *D*, by means of a rubber connection, *C*. Flask *D* is a 100-mL round-bottom, long-neck boiling flask, resting in a suitable heating mantle, *E*.~~

~~The reaction flask is provided with a reflux condenser, *F*, to which is fitted a delivery tube, *G*, of 40-mL capacity, having a stopcock, *H*. The reflux condenser terminates in a trap, *I*, containing 25 g of 20-mesh zinc or tin, which can be connected with an absorption tower, *J*.~~

~~The absorption tower consists of a 45-cm tube fitted with a medium-porosity, sintered-glass disk sealed to the inner part above the side arm and having a delivery tube sealed to it extending down to the end of the tube. A trap, consisting of a bulb of approximately 100-mL capacity, is blown above the sintered-glass disk, and the outer portion of a ground spherical joint is sealed on above the bulb. A 250-mL conical flask, *K*, is connected to the bottom of the absorption tower. The top of the tower is connected to a soda lime tower, *L*, which is connected to a suitable pump to provide vacuum and air supply, the selection of which is made by a three-way stopcock, *M*. The volume of air or vacuum is controlled by a capillary tube regulator or needle valve, *N*.~~

~~All joints are size (35/25), ground spherical type.~~■1S (*USP27*)

Delete the following:

■~~PROCEDURE~~

~~Unless otherwise directed, transfer a specimen of about 250 mg, accurately weighed, into the reaction flask, *D*, add 25 mL of dilute hydrochloric acid (1 in 120), insert several boiling chips, and connect the flask to the reflux condenser, *F*, using phosphoric acid as a lubricant. [NOTE—Stopcock grease may be used for the other connections.] Check the system for air leaks by forcing mercury up into the inner tube of the mercury valve, *B*, to a height of about 5 cm. Turn off the pressure using the stopcock, *M*. If the mercury level does not fall appreciably after 1 to 2 minutes, the apparatus may be considered to be free from leaks. Draw carbon dioxide–free air through the apparatus at a rate of 3000 to 6000 mL per hour. Raise the heating mantle, *E*, to the flask, heat the specimen to boiling, and boil gently for 2 minutes. Turn off and lower the mantle, and allow the specimen to cool for 15 minutes. Charge the delivery tube, *G*, with 23 mL of hydrochloric acid. Disconnect the absorption tower, *J*, rapidly transfer 25.0 mL of 0.25 N sodium hydroxide VS to the tower, add 5 drops of butyl alcohol, and again connect the absorption tower. Draw carbon dioxide–free air through the apparatus at the rate of about 2000 mL per hour, add the hydrochloric acid to the reaction flask through the delivery tube, raise the heating mantle, and heat the reaction mixture to boiling. After 2 hours, discontinue the current of air and heating. Force the sodium hydroxide solution down into the flask, *K*, using gentle air pressure, and then rinse down the absorption tower with three 15-mL portions of water, forcing each washing into the flask with air pressure. Remove the flask, and add to it 10 mL of barium chloride solution (1 in 10). Insert the stopper in the flask, shake gently for about 2 minutes, add phenolphthalein TS, and titrate with 0.1 N hydrochloric acid VS. Perform a blank determination (see *Residual Ti-*~~

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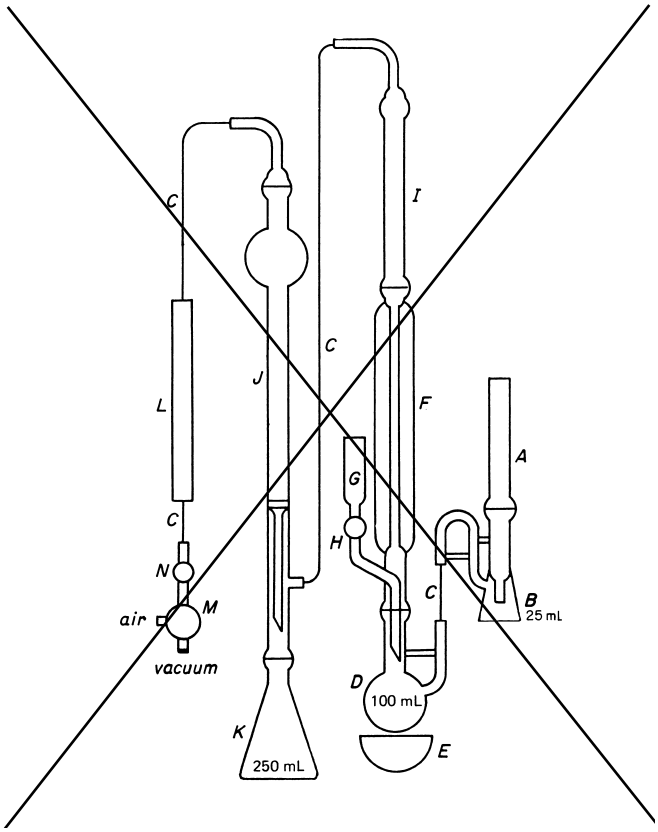
~~*trations* under *Titrimetry* ⟨541⟩. Each mL of 0.25 *N* sodium hydroxide consumed is equivalent to 5.5 mg of carbon dioxide (CO_2).~~ ■1S (*USP27*)

Add the following:

▪APPARATUS

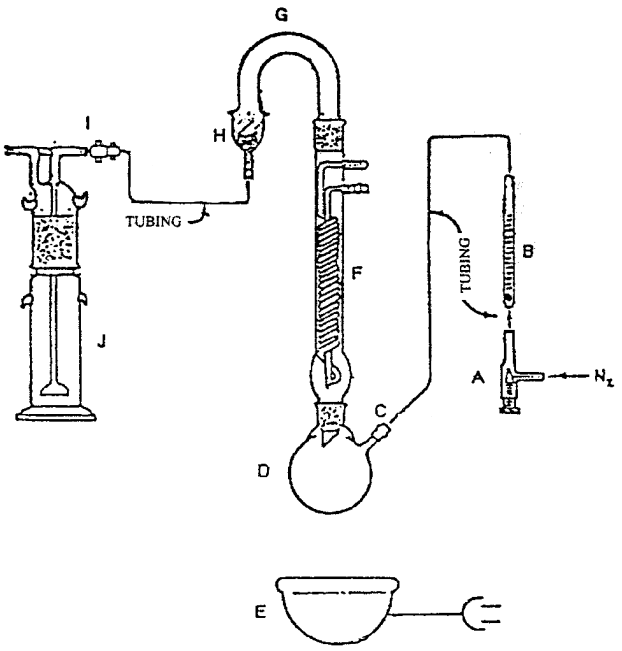
The required apparatus (see *Figure 1*) contains a capillary metering valve, *A*, followed by a flowmeter, *B*, to control and monitor the flow of nitrogen through the system. Halogenated vinyl plastic tubing* and a rubber fitting, *C*, are used to connect the flowmeter to a sidearm of a reaction flask, *D*. Flask *D* is a 250-mL round-bottom, boiling flask, resting in a suitable heating mantle, *E*. Flask *D* is provided with a 225-mm Hopkins coil reflux condenser, *F*. The condenser terminates in a U-shaped trap, *G*, which contains two 25-g bands of 20-mesh zinc, the bands being bounded and separated by three 3-inch plugs of glass wool. The trap terminates in an adapter, *H*, that by means of a halogenated vinyl plastic tubing and a twistcock connector, *I*, connects with a 250-mL gas washing bottle, *J*. The inlet (bubbling) tube extends almost to the bottom of the gas washing bottle, and it terminates in a fritted disc having a coarse porosity. The size of all glass joints is $^{24}/_{40}$, except for the $^{45}/_{50}$ joint of the gas washing bottle. ■1S (*USP27*)

Change to read:



~~Apparatus for Alginates Assay~~

* This type of tubing is commonly referred to as Tygon tubing. This note is added for clarity and it does not constitute USP's endorsement of this product.



■Fig. 1. Apparatus for Alginates Assay■1S (*USP27*)

Add the following:

■SYSTEM SUITABILITY

Using D-glucuronolactone as the standard, proceed as directed for *Procedure*, but do not perform preboiling steps. The system is suitable if the following criteria are met: (1) a blank determination results in a net titration value ~~between 0.2 and 0.6 mL of 0.1 N hydrochloric acid, and (2) the recovery obtained from the standard is between 99.0% and 101.0%.~~ *C*, between 0.02 and 0.06 mEq of 0.1 N hydrochloric acid, calculated as follows:

$$A_b - B_b,$$

in which A_b is the number of mEq of 0.25 N sodium hydroxide in the 25 mL used, and B_b is the number of mEq of 0.1 N hydrochloric acid used in the blank titration; and (2) the percentage of carbon dioxide, CO_2, obtained from the standard is between 24.7% and 25.3%.■1S (*USP27*)

Add the following:

■PROCEDURE

Unless otherwise directed in the individual monograph, transfer a specimen of about 250 mg, accurately weighed, into the reaction flask, *D*, add 50 mL of 0.1 N hydrochloric acid, insert several boiling chips, and connect the flask to the reflux condenser, *F*, using phosphoric acid as a lubricant. [NOTE—Stopcock grease may be used for the other connec-

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tions.] Connect the nitrogen line to the sidearm of the flask, and adjust the flow of cooling water to about 2 liters per minute.

[NOTE—The following preboiling steps, outlined in this paragraph, are optional and need only be performed when the presence of inorganic carbonates is suspected.] Maintain the flow of nitrogen through the apparatus at 90 to 100 mL per minute. Raise the heating mantle, *E*, to the flask, heat the specimen to boiling, and boil gently for 2 minutes. Turn the heat off, lower the mantle, *E*, and allow to cool for about 10 minutes.

Connect the empty gas washing bottle assembly, *J*, and sweep the system with nitrogen at a rate of 90 to 100 mL per minute for 5 minutes. Reduce the nitrogen flow to 60 to 65 mL per minute, add 10 drops of butyl alcohol, 25.0 mL of 0.25 N sodium hydroxide VS, and 50 mL of distilled water into the bottle, rinsing down the inside of the gas washing bottle, and replace the cap. Detach the rubber fitting, *C*, from sidearm, and add 46 mL of hydrochloric acid through the sidearm of the boiling flask. Reattach the nitrogen line, raise the heating mantle, and heat the reaction mixture to boiling. After 2 hours of boiling, increase the nitrogen flow to 90 to 100 mL per minute, discontinue the heating, and lower the mantle. Allow to cool for 10 minutes. Disconnect, and disassemble the gas washing bottle. Using a directed stream of distilled water, thoroughly rinse all parts of the bubbling tube and cap, collecting the washings in the gas washing bottle. Use nitrogen to gently force all water out of the bubbling tube. To the bottle immediately add 10 mL of 10% barium chloride solution and a stirring bar. Insert a tight stopper, and stir gently for 1 minute. Allow to stand for at least 5 minutes. Add three drops of phenolphthalein TS, and titrate with 0.1 N hydrochloric acid VS. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Calculate the percentage of carbon dioxide, CO_2, by the formula:

$$2200[(A - B) - C]/(1000W)(1 - D),$$

in which *A* is the number of mEq of 0.25 N sodium hydroxide in the 25 mL used; *B* is the number of mEq of 0.1 N hydrochloric acid used for the titration of the sample or the standard; *C* is the ~~number of mEq of 0.1 N hydrochloric acid used for the titration of the blank;~~ net titration value calculated in the blank determination. *W* is the weight, in g, of the sample or the standard taken; and *D* is the percentage obtained in the test for *Loss on drying* for the sample or for the standard. ■1S (*USP27*)

BRIEFING

⟨**341**⟩ **Antimicrobial Agents—Content,** *USP 26* page 2064. It is proposed to revise the *Standard Preparation* sections of the test for *Benzyl Alcohol* and the test for *Methylparaben and Propylparaben* under *General Gas Chromatographic Method* to include the use of the Reference Standards USP Benzyl Alcohol RS, USP Methylparaben RS, and USP Propylparaben RS which are now available. In addition, editorial style changes have been made.

(PA7b: B. Davani) RTS—39962-1

Change to read:

GENERAL GAS CHROMATOGRAPHIC METHOD

The general procedures set forth in the following paragraphs are applicable to the quantitative determination of benzyl alcohol, chlorobutanol, phenol, and the methyl, ethyl, propyl, and butyl esters of *p*-hydroxybenzoic acid, the latter being treated as a group, the individual members of which, if present, are capable of separate determination. Prepare the *Internal Standard Solution* and the *Standard Preparation* for each agent as directed individually below. Unless otherwise directed below, prepare the *Test Preparation* from accurately measured portions of the *Internal Standard Solution* and the sample under test, of such size that the concentration of the agent and the composition of the solvent correspond closely to the concentration and composition of the *Standard Preparation*. Suggested operating parameters of the gas chromatograph apparatus are given in the accompanying table, the carrier gas being helium or nitrogen, and the detector being the flame-ionization type.

Suggested Operating Parameters of Gas Chromatograph Apparatus

Agent	Column Size: Length	Column Size: ID	Column Packing Phases and Support	Flow Rate, mL per min.	Column Temperature
Benzyl Alcohol	1.8 m	3 mm	5% G16/S1A	50	140°
Chlorobutanol	1.8 m	2 mm	5% G16/S1A	20	110°
Phenol	1.2 m	3 mm	5% G16/S1A	50	145°
Parabens	1.8 m	2 mm	5% G2/S1A	20	150°

Benzyl Alcohol

Internal Standard Solution—Dissolve about 380 mg of phenol in 10 mL of methanol contained in a 200-mL volumetric flask. Add water to volume, and mix.

Standard Preparation—Dissolve about 180 mg of ~~benzyl alcohol,~~

■USP Benzyl Alcohol RS,■1S (*USP27*)
accurately weighed, in 20.0 mL of methanol contained in a 100-mL volumetric flask. Add *Internal Standard Solution* to volume, and mix.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard Preparation* and the *Test Preparation* into the chromatograph, record the chromatograms with the apparatus adjusted to the parameters set forth in the accompanying table, and measure the areas under the peaks for benzyl alcohol and phenol. Calculate the content, in mg per mL, of benzyl alcohol (C_7H_8O) in the specimen taken by the formula:

$$100(C/V)(p_1/p_2)(P_2/P_1),$$

in which C is the concentration, in mg per mL, of benzyl alcohol in the *Standard Preparation; V* is the volume, in mL, of the specimen under test used in preparing each 100 mL of the *Test Preparation; p_1* and p_2 are the peak areas for benzyl alcohol and phenol, respectively, obtained from the *Test Preparation;* and P_1 and P_2 are the peak areas of benzyl alcohol and phenol, respectively, obtained from the *Standard Preparation*.

Chlorobutanol

Internal Standard Solution—Transfer about 140 mg of benzaldehyde to a 100-mL volumetric flask, add 10 mL of methanol, and swirl to dissolve. Dilute with water to volume, and mix.

Standard Preparation—Transfer about 125 mg of chlorobutanol, accurately weighed, to a 25-mL volumetric flask. Add 2 mL of methanol, swirl to dissolve, dilute with water to volume, and mix. Transfer 5.0 mL of this solution and 5.0 mL of *Internal Standard Solution* to a 25-mL flask, and mix to obtain a solution having a known concentration of about 2.5 mg of chlorobutanol per mL.

Test Preparation—Dilute, if necessary, an accurately measured volume of the specimen under test quantitatively with methanol to obtain a solution containing not more than about 5.0 mg of chlorobutanol per mL. Combine 3.0 mL of this solution with 3.0 mL of *Internal Standard Solution*, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—[NOTE—See accompanying table for column dimensions, column packing phase and support, flow rate, and column temperature.] The injection port temperature is maintained at 180°, and the detector is maintained at 220°. Chromatograph the *Standard Preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for benzaldehyde and 1.0 for chlorobutanol; the resolution, R, between benzaldehyde and the chlorobutanol is not less than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard Preparation* and the *Test Preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of chlorobutanol ($C_4H_7Cl_3O$) in each mL of the specimen under test by the formula:

$$C(L/D)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of chlorobutanol, calculated on the anhydrous basis, in the *Standard Preparation; L* is the labeled quantity, in mg, of chlorobutanol in each mL of the specimen under test; D is the concentration, in mg per mL, of chlorobutanol in the *Test Preparation*, based on the volume of specimen under test taken and the extent of dilution; and R_U and R_S are the ratios of the chlorobutanol peak to the benzaldehyde peak obtained from the *Test Preparation* and the *Standard Preparation*, respectively.

Phenol

Internal Standard Solution—Pipet 1 mL of benzyl alcohol into a 500-mL volumetric flask, add methanol to volume, and mix.

Standard Preparation—Dissolve about 75 mg of phenol, accurately weighed, in 7.5 mL of methanol contained in a 100-mL volumetric flask. Add 20.0 mL of *Internal Standard Solution*, then add water to volume, and mix.

Procedure—Separately inject equal volumes (about 3 µL) of the *Standard Preparation* and the *Test Preparation* into the chromatograph, record the chromatograms with the apparatus adjusted to the parameters set forth in the accompanying table, and measure the areas under the peaks for phenol and benzyl alcohol Calculate the content, in mg per mL, of phenol (C_6H_6O) in each mL of the specimen taken by the formula:

$$100(C/V)(p_1/p_2)(P_2/P_1),$$

in which C is the concentration, in mg per mL, of phenol in the *Standard Preparation; V* is the volume, in mL, of the specimen under test used in preparing each 100 mL of the *Test Preparation; p_1* and p_2 are the peak areas for phenol and benzyl alcohol, respectively, obtained from the *Test Preparation;* and P_1 and P_2 are the peak areas of phenol and benzyl alcohol, respectively, obtained from the *Standard Preparation*.

Methylparaben and Propylparaben

Internal Standard Solution—Place about 200 mg of benzophenone in a 250-mL volumetric flask, dilute with ether to volume, and mix.

Standard Preparation—Place 100 mg of ~~methylparaben~~

■USP Methylparaben RS■1S (*USP27*)
and 10 mg of ~~propylparaben,~~

■USP Propylparaben RS,■1S (*USP27*)
each accurately weighed, in a 200-mL volumetric flask, dilute with *Internal Standard Solution* to volume, and mix. Place 10 mL of this solution in a 25-mL conical flask, and proceed as directed for *Test Preparation*, beginning with "Add 3 mL of pyridine."

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Test Preparation—Pipet 10 mL of the specimen under test and 10 mL of the *Internal Standard Solution* into a small separator. Shake vigorously, allow the layers to separate, draw off the aqueous layer into a second separator, and transfer the ether layer into a small flask through a funnel containing anhydrous sodium sulfate. Extract the aqueous layer with two 10-mL portions of ether, also filtering the extracts through the anhydrous sodium sulfate. Evaporate the combined extracts under a current of dry air until the volume is reduced to about 10 mL, then transfer the residue to a 25-mL conical flask. Add 3 mL of pyridine, complete the evaporation of the ether, and boil on a hot plate until the volume is reduced to about 1 mL. Cool, and add 1 mL of a suitable silylation agent, such as bis(trimethylsilyl)trifluoroacetamide, bis(trimethylsilyl)acetamide, or a mixture of hexamethyldisilazane and trimethylchlorosilane [2:1 or 3:1 (v/v)]. Mix, and allow to stand for not less than 15 minutes.

Procedure—Separately inject equal volumes (2 µL) of the silanized solution from the *Standard Preparation* and the *Test Preparation* into the chromatograph, record the chromatograms with the apparatus adjusted to the parameters set forth in the accompanying table, and measure the areas under the peaks for methylparaben, propylparaben, and benzophenone. Calculate the content, in µg per mL, of methylparaben ($C_8H_8O_3$) in the sample under test by the formula:

$$10(C_M / V)(p_1 / p_3)(P_3 / P_1),$$

in which C_M is the concentration, in µg per mL, of methylparaben in the *Standard Preparation; V* is the volume, in mL, of the specimen taken; p_1 and p_3 are the peak areas for methylparaben and benzophenone, respectively, obtained from the *Test Preparation;* and P_1 and P_3 are the peak areas of methylparaben and benzophenone, respectively, obtained from the *Standard Preparation*. Similarly, calculate the content, in µg per mL, of propylparaben ($C_{10}H_{12}O_3$) in the specimen under test by the formula:

$$10(C_P / V)(p_2 / p_3)(P_3 / P_2),$$

in which C_P is the concentration, in µg per mL, of propylparaben in the *Standard Preparation; V* is the volume, in mL, of the specimen taken; p_2 and p_3 are the peak areas for propylparaben and benzophenone, respectively, obtained from the *Test Preparation;* and P_2 and P_3 are the peak areas of propylparaben and benzophenone, respectively, obtained from the *Standard Preparation*.

Ethylparaben and butylparaben may be determined in a similar manner.

BRIEFING

⟨386⟩ Environmentally Sensitive Preparations. The chapter previously proposed as *Shipping and Storage of Labile Preparations* ⟨1186⟩ (see page 495 of *PF* 28(2) [Mar.–Apr. 2002]), is canceled. A new chapter, *Environmentally Sensitive Preparations* ⟨386⟩, is proposed by the USP Expert Committee on Packaging, Storage, and Distribution. The Expert Committee believes that most articles are uncompromised in the manufacturer's original container when shipped or stored under stressful environmental conditions. However, there is uncertainty about the product's stability when it is removed from the manufacturer's original container and repackaged into another container that may be shipped or stored under stressful environmental conditions. This chapter is intended to focus on this process to ensure that proper communication and requirements are established to protect the integrity of the repackaged product until it reaches the patient.

The test criteria outlined for determining environmentally sensitive preparations are similar to test requirements recommended in the Q1A guidelines of the International Conference on Harmonization. The emphasis is placed on repackaging practices of a repackager, a pharmacist, or a manufacturer and also on the communication channel from the manufacturer to the repackaging pharmacist, and from the pharmacist to the patient. The USP Expert Committee believes that proper communication lines should be maintained from the manufacturer to the repackager and to the pharmacist. Some other aspects of the chapter remain the same. These include the use of temperature monitoring devices as referenced in *Monitoring Devices—Time, Temperature, and Humidity* ⟨1118⟩, and a consideration of the use of unit-of-use packaging (as discussed in *Packaging—Unit of Use* ⟨1136⟩) to obviate any form of repackaging.

In addition, there are some editorial changes, and some modification of the text based on the comments received from the previous publication of ⟨1186⟩. Other changes in this proposed chapter are intended to clarify the content.

(PSD: C. Okeke) RTS—39951-1

Add the following:

■⟨386⟩ ENVIRONMENTALLY SENSITIVE PREPARATIONS

In the interest of ensuring the integrity of a pharmaceutical article as it reaches the patient for a course of treatment, this chapter focuses on preparations that may be repackaged or dispensed in other than the market package so that proper storage and shipment instructions can be included with the official preparation. It is assumed that, as long as these packaged preparations are transported according to the directions in the package insert, the original manufacturer's packages are sufficient for assuring that these requirements are met.

An individual preparation is an *Environmentally Sensitive Preparation* if data indicate the failure of that preparation to conform to a monograph requirement after exposure to one of the following sets of criteria.

CRITERIA TO DETERMINE IF A PRODUCT IS AN ENVIRONMENTALLY SENSITIVE PREPARATION

NOTE—The dosage form may be protected from light during the studies.

1. Use pertinent stability data available on file, or

2. Determine if a preparation meets the test requirements (*a–d*) listed below. If a preparation does not meet a monograph requirement after exposure to conditions specified for requirement *a*, retest as directed for *b*, *c*, or *d*, as appropriate.

a. For any dosage form: 3 months at a temperature of 40 ± 2° and 75 ± 5% relative humidity in the market container, or 30 ± 2° and 60 ± 5% relative humidity for 6 months.

b. For solutions: 3 months at a temperature of 37° to 40 ± 2° and ambient humidity in the market container.

c. For semisolids and heterogeneous liquids, such as creams, transdermal systems, gels, emulsions, and suspensions; and for sterile solids for injection: 6 months at a temperature of 30 ± 2° and 60 ± 5% relative humidity in the market container.

d. For solid oral dosage form: 30 days at a temperature of 25 ± 2° and 60 ± 5% relative humidity in an open dish (i.e., the container without closure, coil, desiccant, or unsealed blisters).

Definitions

For the purpose of this chapter, a packager is defined as one who puts a drug product into a primary container for distribution to patients. A packager may be a repackager, a pharmacist, or a manufacturer.

Labeling, Storage, and Shipping

Decisions regarding the labeling of a product as an *Environmentally Sensitive Preparation* are the responsibility of the packager and are based on the product's characteristics and stability history.

Where data establish that a preparation is an *Environmentally Sensitive Preparation*, any of the following labeling and shipping arrangements are employed, as appropriate, to ensure monograph conformity.

a. The article is shipped in a manner that (1) ensures that its integrity is maintained, and (2) is based on product information, packaging data, and the distribution system used.

b. The article is shipped in suitable appropriate protective packaging—insulated package—that could include foil-laminated polyethylene bags, desiccant containers, or packages of sufficient desiccant capacity.

c. The article is shipped with a validated time–temperature monitoring device (see *Monitoring Devices—Time, Temperature, and Humidity* ⟨1118⟩and other good storage and shipping practice documents). The monitoring device is affixed either to the outer shipping package or to the packaging of individual containers (for example, for mixed shipments).

d. Unopened packages shall be moved through the distribution chain with the monitoring device intact.

e. Where shipping is expected to extend beyond 48 hours, instructions are included, specifying that the article is not to be used if the monitoring device discloses a cumulative history of exposure equivalent to more than 48 hours at or above a temperature of 40°. A manufacturer may make other assurances about packaging and distribution arrangements based on product data and information.

Instructions to the Pharmacist or Repackager

Suitable information must be available to identify an *Environmentally Sensitive Preparation* to the pharmacist or repackager along with appropriate instructions for handling the preparation. For example, the labeling of a manufac-

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turer's multiple-unit package (or market repackage) of a humidity-sensitive preparation may include one or more of the following statements:

a. Do not dispense more than a 30-day supply of the prescription in one multiple-unit container.
b. Dispense it in a desiccant container of sufficient desiccant capacity.
c. Dispense it in a tight or Class A container (see *Containers—Permeation* ⟨671⟩) if it is not dispensed in a market package.
d. "Do not repackage", if the medication is not to be repackaged.
e. Dispense it in a unit-of-use container (see *Packaging—Unit of Use* ⟨1136⟩).
f. Label the patient's containers to state "use the contents within 30 days from the first day that individual container is opened".

Instructions to Institutional Settings

In an institutional setting, store packages of an *Environmentally Sensitive Preparation* at controlled room temperature or according to labeled requirements in the market package. Packages dispensed for use by a particular patient should bear a beyond-use date of 3 months or 90 days and a statement "Store at 20° to 25° (68° F to 77° F)", unless (1) data support other labeling or (2) other manufacturer's recommendations are applicable.

Instructions to the Manufacturer

For an *Environmentally Sensitive Preparation* for which data support other labeling, beyond-use dates, or exposure equivalents, the manufacturer must include labeling and information suitable for optimal handling by the practitioner or pharmacist, by the repackager, and by the patient. Product development or stability data can be used to determine appropriate labeling and shipping statements that will properly inform patients and practitioners.

When repackagers and pharmacists, including hospital, emergency medical services, mail service, Internet-based services, and other practitioners, request information about product behavior upon exposure to various temperature and humidity conditions, pharmaceutical manufacturers are encouraged to provide such information if available.

Exemptions

1. The following preparations are exempt from the above considerations: those labeled that they must be stored and transported refrigerated or frozen; labeled radiopharmaceuticals; and those shipped and received in not more than the time period specified on the outer package, provided data are available to show that the stability of the article is not compromised during that period under the expected conditions of temperature and/or humidity.
2. For classifying a preparation as an *Environmentally Sensitive Preparation*, the general chapter *Uniformity of Dosage Units* ⟨905⟩ does not apply.■1S (*USP27*)

BRIEFING

⟨**401**⟩ **Fats and Fixed Oils,** *USP 26* page 2086. It is proposed to add two general procedural sections, *Anisidine Value* and *Total Oxidation Value*, to this general test chapter because these procedures are proposed for several monographs containing polyunsaturated fatty acids.

(DSN: G. Giancaspro; ETM: C. Sheehan) RTS—39705-4

Add the following:

▪ANISIDINE VALUE

The anisidine value is defined as 100 times the optical density measured in a 1-cm cell of a solution containing 1 g of the substance to be examined in 100 mL of a mixture of solvents and reagents according to the method described below. [NOTE—Carry out the operations as rapidly as possible, avoiding exposure to actinic light.]

Test Solution A—Dissolve 0.500 g of the substance to be examined in isooctane, and dilute with the same solvent to 25.0 mL.

Test Solution B—To 5.0 mL of *Test Solution A* add 1.0 mL of a 2.5 g per L solution of *p*-anisidine in glacial acetic acid, shake, and store protected from light.

Standard Solution—To 5.0 mL of isooctane add 1.0 mL of a 2.5 g per L solution of *p*-anisidine in glacial acetic acid, shake, and store protected from light.

Procedure—Measure the absorbance of *Test Solution A* at 350 nm using isooctane as the blank. Measure the absorbance of *Test Solution B* at 350 nm exactly 10 minutes after its preparation, using the *Standard Solution* as the compensation liquid. Calculate the Anisidine Value from the expression:

$$\frac{25(1.2A_s - A_b)}{m},$$

in which A_S is the absorbance of *Test Solution B* at 350 nm; A_b is the absorbance of *Test Solution A* at 350 nm; and m is the weight, in g, of the substance to be examined in *Test Solution A*.▪1S (*USP27*)

Add the following:

▪TOTAL OXIDATION VALUE (TOTOX)

Total Oxidation Value is defined by the formula:

$$2PV + AV,$$

in which *PV* is the *Peroxide Value*, and *AV* is the *Anisidine Value*.▪1S (*USP27*)

BRIEFING

⟨429⟩ Light Diffraction Measurement of Particle Size, page 484 of *PF* 29(2) [Mar.–April 2003]. This new general test chapter, which was previously presented in 29 (2) is republished with additional revisions to clarify the text of this chapter: (1) Additional information on the use of microscopy to determine agglomerates is added to the opening paragraphs; (2) An elaboration of the use of the Mie theory is added under *Selection of an Appropriate Optical Model*; and (3) Recommendations to state the cell type, sample state and preparation, and the make and model of the equipment are included in the section *Conversion of Scattering Pattern into Particle Size Distribution*.

(ETM: J. Lane) RTS—39926-1

Add the following:

▪⟨429⟩ LIGHT DIFFRACTION MEASUREMENT OF PARTICLE SIZE

Light diffraction is one of the most widely used techniques for measuring the size of ~~particles in the range of 0.1 µm to 3 mm.~~ a wide range of particles from very fine to very coarse. ~~This popularity is partly due to the way precise measurements can be made quickly and easily. The method is also popular due to the flexibility of the technique, particularly the way.~~ The method is popular because it is quick and easy to use, flexible, and it can be adapted to measure samples presented in various physical forms. The method depends on ~~analyzing~~ the analysis of the diffraction pattern produced when particles are exposed to a collimated

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beam of light. As the patterns are characteristic of the particle size, mathematical analysis can produce an accurate, ~~reproducible~~ repeatable picture of the size distribution.

This chapter provides guidance on the measurement of size distributions of particles in any phase system (e.g., powders, sprays, aerosols, suspensions, emulsions, and gas bubbles in liquids) through analysis of their angular light-scattering patterns. ~~The method is applicable to particle sizes ranging from approximately 0.1 µm to 3 mm.~~ Traditionally, the measurement of particle size using laser diffraction has been limited to particles in the range 0.1 µm to 3 mm. Due to recent advances in optics and lens and equipment design and construction, newer instruments are routinely capable of exceeding this range (e.g., 0.1 µm to 8 mm). It is the responsibility of the user to demonstrate the applicability of the instrument for its intended use and to validate any method prior to its adoption for routine use.

For nonspherical particles, an equivalent-sphere size distribution is obtained because the technique uses the assumption of spherical particles in its optical model. The resulting particle size distribution may be different from those obtained by methods based on other physical principles (such as sedimentation or sieving). The laser diffraction technique cannot distinguish between scattering by single particles and scattering by clusters of primary particles forming an agglomerate or an aggregate. If the presence of aggregates is suspected, this can be investigated using other techniques such as microscopy.

The laser diffraction technique is based on the phenomenon that particles scatter light in all directions with an intensity pattern that is dependent on particle size. All present instruments assume a spherical shape for the particles. Historically, the ~~laser diffraction technique started by taking~~ early laser diffraction instruments used only scattering at small angles ~~into consideration~~ and, thus, has been known by the following names: Fraunhofer diffraction, (near-) forward light scattering, and low-angle laser light scattering (LALLS).

However, the technique sincehas been broadened to include light scattering in a wider angular range ~~and~~ by application of the Mie theory, in addition to ~~approximating other techniques such as that from Fraunhofer~~ the Fraunhofer approximation and anomalous diffraction.

The measurement of particle size is an important aspect in the characterization of raw materials and drug formulations. To monitor production and particle stability, efficient and rapid methods for particle sizing are needed. The electronic measurement of samples offers a convenient solution to this problem. However, the electronic measurement will often have to be accompanied by microscopical investigation to determine the type of particles being investigated. Modern drug formulations may also be particulate formulations where the particle size will be below 100 µm, and reliable and reproducible methods are needed for the quality control of these drug products.

PRINCIPLE

A representative sample, dispersed at an adequate concentration in a suitable liquid or gas, is passed through the beam of a monochromatic light source, usually from a laser. The light scattered by the particles at various angles is measured by a multi-element detector, and numerical values relating to the scattering pattern are then recorded for subsequent analysis. These numerical scattering values are then transformed, using an appropriate optical model and mathematical procedure, to yield the proportion of total volume to a discrete number of size classes forming a volumetric particle size distribution (e.g., x_{50} describes a particle diameter corresponding to 50% of the cumulative undersize distribution).

APPARATUS

A typical setup for a laser diffraction instrument is shown in *Figure 1*.

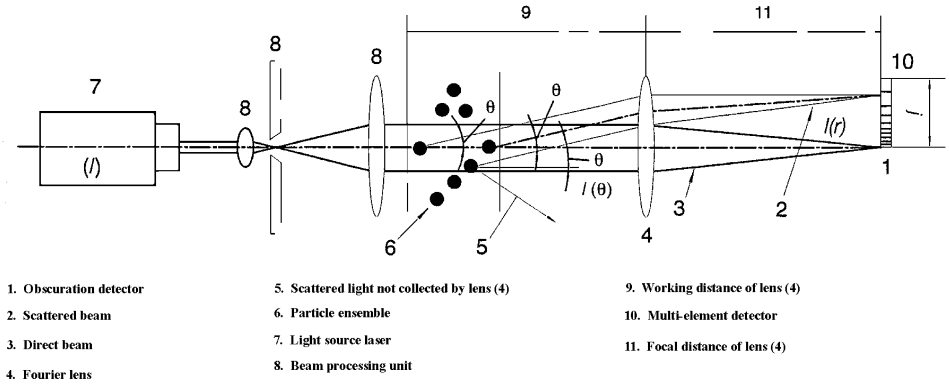

Fig. 1. Typical setup for a laser diffraction instrument.

A representative sample, dispersed at an adequate concentration, is passed through the light beam in a measuring zone by a transporting ~~medium~~ fluid (gas or liquid); this measuring zone should be within the working distance of the lens used. In some cases the particle stream in a process is illuminated directly by the laser beam for measurement, as in the case of sprays, aerosols, and air bubbles in liquids. In other cases (such as emulsions, pastes, and powders), representative samples can be dispersed in suitable liquids. Often dispersants (such as wetting agents or stabilizers) or mechanical forces (such as agitation or ultrasonication), or both, are applied to deagglomerate particles and to stabilize the dispersion. For these liquid dispersions, a recirculating system is most commonly used, consisting of an optical measurement cell, a dispersion bath (usually equipped with stirrer and ultrasonic elements), a pump, and tubing.

Dry powders can also be converted into aerosols through ~~application~~ the use of dry powder dispersers, which apply mechanical forces for deagglomeration. In this case, a dosing device feeds the disperser with a constant mass flow of sample. The disperser uses the energy of compressed gas or the differential pressure to a vacuum to disperse the particles. It outputs an aerosol that is blown through the measuring zone, usually into the inlet of a vacuum pipe that collects the particles.

There are two positions in which the particles can enter the laser beam. In the conventional case, the particles enter the parallel beam before and within the working distance ofthe collecting lens. In the so-called reversed Fourier optics case, the particles enter behind the collecting lens, and thus in a converging beam.

The advantage of the conventional setup is that a reasonable path length for the sample is allowed within the working distance of the lens. The second setup allows only small path lengths but enables measurement of scattered light at larger angles, which is useful when ~~submicrometer~~ submicron particles are present.

The interaction of the incident light beam with the dispersed particles results in a scattering pattern with different light intensities at various angles. The total angular intensity distribution, consisting of both direct and scattered light, is then focused by a positive lens or an assembly of lenses onto a multi-element detector. The lens(es) provide(s) for a scattering pattern which, within limits, is not dependent upon the location of the particles in the light beam. Thus the con-

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tinuous angular intensity distribution is converted into a discrete spatial intensity distribution on a set of detector elements.

It is assumed that the recorded scattering pattern of the particle ensemble is identical to the sum of the patterns from all individual single scattering particles presented in random relative positions. Note that only a limited angular range of scattered light is collected by the lens(es), and thus by the detector.

PREPARATION OF THE SAMPLE

Prepare a representative sample of suitable volume for the measurement by an adequate sample splitting technique.

Sprays, aerosols, and gas bubbles in liquid should be measured directly, provided that their concentration is at an ~~adequate~~ appropriate level, since sampling or dilution is generally impossible without altering the particle size distribution.

The dispersion procedure is adjusted to the purpose of the measurement: for example, ~~one must decide~~ whether agglomerates should be detected or broken down to primary particles.

For the development of a method, it is necessary to check that comminution of the primary particles does not occur, and conversely that a good dispersion of the agglomerates has been achieved. ~~This~~ The dry particles may be examined microscopically before and after the addition and dispersion of aliquots of the dispersing liquid to determine if the particle size has changed, and if the agglomerates are dispersed but the primary particles are not fractured. The effect of the dispersion process can usually be ~~done~~ checked by changing the dispersing energy and monitoring the change of the size distribution. The measured size distribution does not change significantly if the sample is well dispersed and the particles are neither fragile nor soluble. Microscopy may also be used to investigate primary particle comminution and adequacy of dispersion.

Dispersion Liquids

A variety of liquids are available for the dispersion of powders and must have the following characteristics:

— be transparent at the laser wavelength and free from air bubbles or other particles,
— be compatible with the materials used in the instrument (O-ring, tubing, etc.),
— not dissolve or alter the size of the particulate materials,
— favor easy and stable dispersion of the particulate material,
— have suitable viscosity to enable calculation,
— have a refractive index ~~differing~~ that differs from that of the material (for the Mie calculation), and
— not be hazardous to health and meet safety requirements.

A low-foaming surfactant and dispersant may be used to facilitate the wetting of the particles and to stabilize the dispersion. A preliminary check on the dispersion quality can be made by visual or microscopic inspection of the suspension.

If very small samples are required, it is also possible to take fractional samples out of a well-mixed sample paste if the material is neither fragile nor soluble. The consistency of the paste then prevents segregation errors. The pastes are formed by adding dispersant to the sample dropwise, while mixing it with a spatula. As long as the mixture forms lumps, single drops should be added while continuing the mixing after each drop. A good consistency for the paste is one like honey or toothpaste. If the paste becomes too fluid by mistake, it cannot be used, and a new preparation is initiated.

Alternatively, a concentrated suspension may be prepared. While stirring this concentrated suspension, a small aliquot is removed and transferred to the optical measurement cell containing the blank dispersing medium. Care must be taken to ensure the complete transfer of the sample and that settling of the larger particles does not occur.

Where a dispersant that does not dissolve the particles cannot be found, it may be possible to use a prefiltered, saturated solution of the sample in the dispersing solvent as the dispersant. Such a saturated solution may be produced by stirring an excess of sample in the dispersing solvent for several hours. For weak acids and weak bases, buffering of the dispersing solvent at low or high pH, respectively, can assist in identifying a suitable dispersant. The saturated medium is filtered using a membrane filter to remove any undissolved sample before use. This approach is not suitable if the sample forms a more viscous concentrated solution.

Dispersion Gases

For dry dispersion and spray applications, a compressed gas is sometimes used. If used, it is essential that it is free from oil, water, and particles. To achieve this, a dryer with a filter is required. Any vacuum unit is located away from the measurement zone, so that the output of the hot air does not reach the measuring zone. Avoid drafts in order to avoid unstable particulate streams.

Concentration

The particle concentration in the dispersion should be above a minimum level, which for many instruments will correspond to about 5% obscuration, in order to produce an acceptable signal-to-noise ratio in the detector. Likewise, it should be below a maximum level in order to avoid multiple scattering (for example, 35% above 20 μm and 15% below 20 μm).

The ~~range of concentrations~~ optimum concentration is influenced by the laser beam width, the path length of the measurement zone, the optical properties of the particles, and the sensitivity of the detector elements. In view of the above, perform measurements at different particle concentrations in order to decide on the optimum concentration range that achieves the required obscuration for any typical sample of material.

MEASUREMENT

Setting Up the Instrument and Blank Measurement

After selection of the appropriate particle size range and proper alignment of the optical part of the instrument, a blank measurement is performed in which a particle-free dispersion medium is used.

Measurement of the Scattering of Dispersed Sample(s)

Generally, ~~a measuring time allowing for~~ a large number of detector scans or sweeps at short time intervals is used (typically some 2 seconds or 1000 sweeps). For each detector element an average signal is calculated, sometimes together with its standard deviation. Data are stored in the computer memory. The magnitude of the signal from each detector element depends upon the detection area, the light intensity, and the quantum efficiency. The coordinates (size and position) of the detector elements, together with the focal distance of the lens, determine the region of scattering angles for each element. ~~Generally all these~~ These factors are factory-determined and stored in the computer.

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Most instruments also measure the intensity of the central laser beam. The difference between a dispersed sample and a blank experiment is given as an obscuration value, which is indicative of the total amount of scattering light and the particle concentration.

Selection of an Appropriate Optical Model

Most often either the Fraunhofer approximation or the Mie theory is used, ~~Sometimes other approximating theories are applied for calculation of the scattering matrix.~~ though other approximations are sometimes applied for calculation of the scattering matrix. Below approximately 25 µm, the differences between the optical models become more significant. In this size range, the proper application of the Mie theory (assuming accurate real and imaginary refractive index values) provides the greatest accuracy. When using the Mie theory, the refractive indices of particulate and medium, or their ratio, are entered into the instrument to allow calculation of the model matrix. Often, small values of the imaginary part of the refractive index (about 0.01–0.1) are applied to cope with the surface roughness of the particles.[1] In order to obtain traceable results, it is essential that the refractive index values used are reported.

Conversion of Scattering Pattern into Particle Size Distribution

This deconvolution step is the inverse of the calculation of a scattering pattern for a given particle size distribution. The fact that rapidly measured data always contain some random and systematic errors may cause erroneous size distribution results. Several mathematical procedures have been developed for use in the different instruments available. They ~~contain~~ allow for some weighting of deviations between measured and calculated scattering patterns (such as least squares), some constraints (such as non-negativity for amounts of particles), or (or in combination with) some smoothing of the size distribution curve. A new procedure uses the observed fluctuations of the detector signals to introduce proper weighting of these data and to calculate confidence intervals for the particle size distribution.

The algorithms used are specific to each make and model of equipment and are proprietary. The differences in the algorithms between different instruments can give rise to differences in the particle size statistics. For this reason, when reporting the particle size distribution and statistics for a given material, also report the cell type, sample state and preparation, together with the make and model of the equipment.

Replicates

The required precision of the method is dependent on the characteristics of the material (milled versus not milled, robust versus fragile), and also on the requirements of the application (formulation type and technique). Appropriate measurement conditions are established experimentally, in relation to the desired precision. In general, at least three different representative samples from the same batch are measured. The repeatability of ~~characteristic particle size in size distributions~~ the particle size distribution parameter is as follows: for any ~~chosen~~ central value of the distribution, for example the median ~~size~~ (x_{50}), the coefficient of variation is ~~smaller~~ less than 10%. ~~Values at the sides of the distribution, for example x_{10} and x_{90}, have a coefficient of variation not exceeding.~~ For values away from the center of the distribution, for example x_{10} and x_{90}, the coefficient of variation cannot exceed 15%. Below 10 µm, these maximum values are doubled.

[1] Small differences in the assumed complex refractive index may cause significant differences in the resulting particle size distributions.

System Suitability

The system suitability test is used to verify that the precision and accuracy are adequate for the analysis to be done. The test is based on the concept that the equipment, electronics, and analytical operations constitute an integral system that can be evaluated as such. This can be done by measuring at regular time intervals a control material of known size distribution. In general, unless otherwise specified in the individual monograph, the mean values of three measurements must deviate from the established value by less than 10% for x_{50}, and by less than 15% for x_{10} and x_{90}. Below 10 µm, these maximum values ~~must be~~ are doubled.

Reporting of Results

The distribution statistics are usually reported by the instrument data system. Most common parameters are calculated from the cumulative distribution by interpolation. Percentile sizes, x_m, represent the particle size in relation to which m percent of the distribution is smaller. (The notation d_m is also used and is equivalent to x_m.) Q_y represents the percent smaller than y microns. Mean sizes, such as $D_{4,3}$, the arithmetic volume mean diameter, can also be calculated by representing the distribution as a collection of spherical particles with diameters of the size band midpoints. Unless otherwise stated, parameters are calculated on the volume or mass basis.

~~VALIDATION~~ QUALIFICATION

Calibration

Laser diffraction systems are based on the direct measurement of the diffraction pattern of particles, but with idealized properties of the particles. Thus, calibration in the strict sense is not required. However, it is still necessary and desirable to confirm the correct operation of the instrument with a ~~validation~~ qualification procedure.

Accuracy and Repeatability

~~Primary validation~~ Primarily, qualification validation can be made with any certified or standard reference material, acceptable for use in the particular ~~industries.~~ industry. Here, the total measurement procedure is being examined, including sampling, sample dispersion, sample transport through the measuring zone, measurement, and the deconvolution procedure. It is essential that the total operational procedure is adequately described in full detail.

Certified or standard reference materials consisting of a known distribution having a range of spherical particles over one decade of size are preferred. They ~~must be~~ are certified to mass percentage by an absolute technique, if available, and used in conjunction with an agreed, detailed operational procedure. It is essential that the real and imaginary part of the complex refractive index are precisely specified for the material if the Mie theory is applied in data analysis.

The response of a laser diffraction instrument is considered adequate if the mean value of x_{50} obtained from at least three independent measurements ~~deviates by less than 3% from the certified range of values of the certified or standard reference material (i.e., the mean value together with its standard deviation).~~ does not exceed the certified range of values of the certified or standard reference material by more than 3%. The mean values for x_{10} and x_{90} must ~~deviate by less than 5% from the certified range of values.~~ not exceed the certified range of values by more than 5%. For repeatability, the coefficient of variation must be ~~smaller~~ less than 3% for x_{50} and ~~smaller~~ less than 5% for x_{10} and x_{90}. Below 10 µm, these maximum values ~~must be~~ are doubled.

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Although the use of spherical materials is preferable, nonspherical ones may also be used. Preferably, these have certified or typical values coming from laser diffraction analyses according to an agreed, detailed operational procedure. If the reference values come from methods other than laser diffraction, a significant bias may result. The reason for this bias is that the different principles applied in the various methods may lead to different ~~sensitivity to the properties,~~ responses to the particles, and thus to different equivalent-sphere diameters for the same nonspherical particle.■1S (*USP27*)

BRIEFING

⟨467⟩ Organic Volatile Impurities, *USP 26* page 2077; **General Notices,** *USP 26* page 3; **⟨1086⟩ Impurities in Official Articles,** *USP 26* page 2331. General Chapter *Organic Volatile Impurities* ⟨467⟩, *General Notices* (*Foreign Substances and Impurities*), and General Chapter *Impurities in Official Articles* ⟨1086⟩ are being revised to provide consistency with the ICH Q3C Guideline (*Impurities: Guideline for Residual Solvents*) and to further harmonize with the *European Pharmacopoeia* (*2.4.24 Identification and control of residual solvents* and *5.4 Residual solvents*).

The current USP General Chapter *Organic Volatile Impurities* ⟨467⟩ is inconsistent with the ICH Q3C Guideline because of terminology and options for describing limits of Class 2 residual solvents. With respect to terminology, both the *General Notices* (*Foreign Substances and Impurities*) and General Chapter ⟨467⟩ use "organic volatile impurities" whereas the ICH Q3C Guideline uses "residual solvents". For options describing limits of Class 2 residual solvents, the ICH Q3C Guideline provides two options: Option 1, where concentration limits, based on defined permitted daily exposure, are applied to each individual substance, excipient, or product, and Option 2, where the drug product is tested or by summing the amounts of a residual solvent present in each of the components. In contrast, the current USP General Chapter ⟨467⟩ only provides test procedures for organic volatile impurities in Pharmacopeial articles.

In addition, the procedures in USP General Chapter ⟨467⟩ for organic volatile impurities do not provide adequate sensitivity for the determination of benzene. The chromatographic systems A and B specified in the *European Pharmacopoeia* General Chapter *2.4.24 Identification and control of residual solvents*, and in this revision proposal, provide the requisite sensitivity.

USP intends to propose revisions to the USP organic volatile impurities policy in three stages. In the first stage, the current USP General Chapter ⟨467⟩ will be revised, as shown in this proposal, to incorporate the ICH Q3C Guideline and the *European Pharmacopoeia* procedures for *2.4.24 Identification and control of residual solvents* and *5.4 Residual solvents*. Revisions are also proposed in this stage for USP General Chapter *Impurities in Official Articles* ⟨1086⟩ and for the *USP General Notices and Requirements* (*Foreign Substances and Impurities*) to reflect the ICH Q3C Guideline. These stage 1 proposals are published elsewhere in this number of *PF*. With the adoption of these proposals, the residual solvents will be controlled by the requirements for residual solvents in General Chapter ⟨467⟩ and the information in General Chapter ⟨1086⟩ together with the requirements in the *USP General Notices* for *Residual Solvents* under *Foreign Substances and Impurities*. Stage 2 of this revision process will involve publication of a request for data to support replacement of *Organic Volatile Impurities* ⟨467⟩ specifications with Residual Solvents specifications in specific monographs. This request will appear in the *Policies and Announcements* section of a forthcoming issue of *PF*. Also in stage 2, USP will propose a change in the title of General Chapter ⟨467⟩ from *Organic Volatile Impurities* to *Residual Solvents*. In stage 3, USP will propose deletion of analytical Methods I, IV, V, and VI from General Chapter ⟨467⟩. This proposal will be made because Methods I, V, and VI are not suitable for analyzing benzene at the required level and Method IV is quite similar to the EP System A procedure.

Comments regarding this proposal are invited and should be submitted by November 28, 2003.

(PA2: W. Paul) RTS—35842-1

Change to read:

⟨467⟩ ORGANIC VOLATILE IMPURITIES

~~NOTE—The requirements for limit of benzene are removed from any article for which *Organic Volatile Impurities* ⟨467⟩ is specified in a *USP* or *NF* monograph except where a specific limit for benzene is included in an individual monograph.~~

~~The following methods are presented for determination of organic volatile impurities in Pharmacopeial articles. The particular method to be used and any necessary method details and variations are specified in the individual monographs.~~

~~Unnecessary testing may be avoided where a manufacturer has assurance, based on knowledge of the manufacturing process and controlled handling, shipping, and storage of an article, that there is no potential for specific toxic solvents to be present and that the material, if tested, will comply with established standards. In particular, items shipped in nontight containers, within the regulations that apply to food additives,* can be considered not to have acquired toxic solvents during transportation. (See *Procedures* under *General Notices*.) [NOTE—The organic-free water specified in the following methods produces no significantly interfering peaks when chromatographed.]~~

~~**Ethylene Oxide**—The test for ethylene oxide is conducted only where specified in the individual monograph. The standard solution parameters and the method for determination are described in the individual monograph. Unless otherwise specified in the individual monograph, the limit is 10 µg per g.~~

~~METHOD I~~

~~A gas chromatograph capable of temperature programming and equipped with a wide-bore wall-coated open-tubular column and a flame-ionization detector is used in the following procedure.~~

~~**Standard Solution**—Prepare a solution, in organic-free water or the solvent specified in the monograph, containing, in each mL, 12.0 µg of methylene chloride, 7.6 µg of 1,4-dioxane, 1.6 µg of trichloroethylene, and 1.2 µg of chloroform. [NOTE—Prepare fresh daily.]~~

~~* 49 C.F.R. 177.841 (e)(1), (3) (1995).~~

Test Solution— Dissolve in organic-free water or the solvent specified in the monograph, an accurately weighed portion of the material to be tested to obtain a final solution having a known concentration of about 20 mg of the bulk pharmaceutical chemical per mL.

Chromatographic System (see *Chromatography* ⟨621⟩)— The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused-silica analytical column coated with a 5-µm chemically cross-linked G27 stationary phase, and a 0.53-mm × 5-m silica guard column deactivated with phenylmethyl siloxane. The carrier gas is helium with a linear velocity of about 35 cm per second. [NOTE— When a makeup gas is used, nitrogen is recommended.] The injection port temperature and the detector temperature are maintained at 70° and 260°, respectively. The column temperature is programmed according to the following steps. It is maintained at 35° for 5 minutes, then increased to 175° at a rate of 8° per minute, followed by an increase to 260° at a rate of 35° per minute and maintained for at least 16 minutes.

Inject the *Standard Solution*, and record the peak responses as directed for *Procedure:* a suitable system is one that yields chromatograms in which all of the components in the *Standard Solution* are resolved; the resolution, *R*, between any two components is not less than 1.0; and the relative standard deviation of the individual peak responses from replicate injections is not more than 15%.

Procedure— Separately inject equal volumes (about 1 µL) of the *Standard Solution* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the peak responses.

Identify, based on retention time, any peaks present in the chromatogram of the *Test Solution*. The identity and peak response in the chromatogram may be established as being from any of the organic volatile impurities listed in *Table 1* or from some other volatile impurity eluting with a comparable retention time by mass spectrometric relative abundance methods or by the use of a second validated column containing a different stationary phase.

Table 1

Organic Volatile Impurity	Limit (µg per g)
Chloroform	60
1,4-Dioxane	380
Methylene Chloride	600
Trichloroethylene	80

Unless otherwise specified in the individual monograph, the amount of each organic volatile impurity present in the material does not exceed the limit given in the accompanying table.

METHOD IV

Standard Solution— Prepare as directed for *Standard Solution* in *Method I*. Pipet 5 mL of the solution into a vial fitted with a septum and crimp cap, containing 1 g of anhydrous sodium sulfate, and seal. Heat the sealed vial at 80° for 60 minutes.

Test Solution— Transfer 100 mg, accurately weighed, of the material under test to a vial, add 5.0 mL of water, or the solvent specified in the monograph, and 1 g of anhydrous sodium sulfate, and seal with a septum and crimp cap. Heat the sealed vial at 80° for 60 minutes, or as specified in the individual monograph.

Chromatographic System and Procedure— [NOTE— The use of headspace apparatuses that automatically transfer a measured amount of headspace is allowed.] Proceed as directed under *Method V*, except to inject, using a heated gas-tight syringe, 1 mL of the headspace. Also, the use of a guard column in this headspace procedure is not necessary.

METHOD V

Standard Solution and Test Solution— Proceed as directed under *Method I*.

Chromatographic System (see *Chromatography* ⟨621⟩)— The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused-silica analytical column coated with a 3.0-µm G43 stationary phase, and a 0.53-mm × 5-m silica guard column deactivated with phenylmethyl siloxane. The carrier gas is helium with a linear velocity of about 35 cm per second. The injection port and detector temperatures are maintained at 140° and 260°, respectively. The column temperature is programmed according to the following steps. It is maintained at 40° for 20 minutes, then increased rapidly to 240° and maintained for 20 minutes.

Inject the *Standard Solution*, and record the peak responses as directed for *Procedure:* a suitable system is one that yields chromatograms in which all of the components in the *Standard Solution* are resolved; the resolution, *R*, between any two components is not less than 3; and the relative standard deviation of the individual peak responses from replicate injections is not more than 15%.

Procedure— Proceed as directed under *Method I*, the injection volume being about 1 µL.

METHOD VI

Standard Solution and Test Solution— Proceed as directed under *Method I*.

Chromatographic System (see *Chromatography* ⟨621⟩)— The gas chromatograph is equipped with a flame-ionization detector. The column and column temperature conditions, as chosen from *Table 2*, are specified in the individual monograph. The carrier gas, linear velocity or flow rate, detector, and injector temperatures are appropriate to the column dimensions and column temperatures chosen in *Table 2*.

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Table 2

Chromatographic Conditions	USP Column Designation	Column Size	Column Temperature
A	S3	3-mm × 2-m	190°
B	S2	3-mm × 2.1-m	160°
C	G16	0.53-mm × 30-m	40°
D	G39	3-mm × 2-m	65°
E	G16	3-mm × 2-m	70°
F	S4	2-mm × 2.5-m	Hold 120° (35 min.) Gradient 120°–200° (2°/min.) Hold 20 min.
H	G14	2-mm × 2.5-m	Hold 45° (3 min.) Gradient 45°–120° (8°/min.) Hold 15 min.
I	G27	0.53-mm × 30-m	Hold 35° (5 min.) 35°–175° (8°/min.) 175°–260° (35°/min.) Hold 16 min.
J	G16	0.33-mm × 30-m	Hold 50° (20 min.) 50°–165° (6°/min.) Hold 20 min.

Inject the *Standard Solution*, and record the peak responses as directed for *Procedure*: a suitable system is one that yields the chromatograms in which all of the components in the *Standard Solution* are resolved; the resolution, *R*, between any two components is not less than 1.0; and the relative standard deviation of the individual peak responses from replicate injections is not more than 15%.

Procedure—Proceed as directed under *Method I*, the injection volume being about 1 µL.

METHOD FOR METHYLENE CHLORIDE IN COATED TABLETS

The limit of methylene chloride is 500 µg per day, based on the maximum labeled daily dose.

Stock Solution—Accurately transfer 3.8 µL (the equivalent of 5 mg) of methylene chloride into a 1000-mL volumetric flask, dilute with organic-free water to volume, and mix.

Standard Solution—[NOTE—Film-coated tablets are to be incised prior to preparation of the solution.] Transfer a number of whole tablets, equivalent to about 1 g, to a glass-stoppered flask. Pipet 20 mL of *Stock Solution* into the flask, insert the stopper tightly, place in an ultrasonic bath until the tablets are completely disintegrated, and centrifuge the resultant solution. Pipet 2 mL of the clear supernatant into a vial equipped with a septum and a metallic crimp cap, and seal. Place the vial in a water bath maintained at 85°, and allow to stand for about 20 minutes.

Sample Solution—Prepare in the same manner as the *Standard Solution* except use 20 mL of organic-free water instead of 20 mL of *Stock Solution*.

System Suitability Solution—Prepare a solution in organic-free water containing 5 µg per mL each of alcohol and methylene chloride. Transfer 2.0 mL to a vial equipped with a septum and a metallic crimp cap, and seal. Place the vial in a water bath at 85°, and allow to stand for 20 minutes.

Chromatographic System—(see *Chromatography* ⟨621⟩)—[NOTE—A headspace apparatus that automatically transfers a measured amount of headspace can be used.] Proceed as directed under *Method V*, except to inject, using a heated gas-tight syringe, 1 mL of headspace. Inject 1 mL of the gaseous phase of the *System Suitability Solution* as directed for *Procedure*: the resolution, *R*, between alcohol and methylene chloride is not less than 1.5. The relative standard deviation of replicate injections of the *Standard Solution* is not more than 10%.

Procedure—Separately inject equal volumes (about 1 mL) of the gaseous headspace of the *Standard Solution* and the *Sample Solution* into the chromatograph. Record the chromatograms and measure the peak responses. Determine, based on a retention time comparison, if methylene chloride is detected in the *Sample Solution*. Determine the amount, in µg per tablet, of any methylene chloride detected. Calculate the maximum amount, in µg per tablet per day, of methylene chloride allowed in the dosage unit using the following formula:

$$\text{maximum allowed amount (µg/day/tablet)} = \frac{500\,(\text{µg/day})}{\text{maximum daily dose (mg)}} \times \text{labled tablet strength (mg/tablet)}$$

The amount of methylene chloride detected per tablet does not exceed the calculated maximum allowed amount.

▪RESIDUAL SOLVENTS LIMITS

For pharmacopeial purposes, residual solvents in pharmaceuticals are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The residual solvents are not completely removed by practical

manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance or an excipient may enhance the yield, or determine characteristics such as crystal form, purity, and solubility. Therefore, the solvent may sometimes be a critical element in the synthetic process. This General Chapter does not address solvents deliberately used as excipients nor does it address solvates. However, the content of solvents in such products should be evaluated and justified.

Because residual solvents do not provide therapeutic benefit, they should be removed, to the extent possible, to meet ingredient and product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. Solvents that are known to cause unacceptable toxicities (Class 1, *Table 1*) should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment. Solvents associated with less severe toxicity (Class 2, *Table 2*) should be limited in order to protect patients from potential adverse effects. Ideally, less toxic solvents (Class 3, *Table 3*) should be used where practical. The complete list of solvents included in this General Chapter is given in Appendix 1. These tables and the list are not exhaustive. Where other solvents have been used, based on approval by the competent regulatory authority, such solvents may be added to the tables and list.

Testing of drug substances, excipients, and drug products for residual solvents should be performed when production or purification processes are known to result in the presence of such residual solvents. It is only necessary to test for residual solvents that are used or produced in the manufacture or purification processes.

Although manufacturers may choose to test the drug product, a cumulative procedure may be used to calculate the residual solvent levels in the product from the levels in its ingredients. If the calculation results in a level equal to or below that recommended in this General Chapter, no testing of the drug product for residual solvents needs to be considered. If, however, the calculated levels are above the recommended level, the drug product should be tested to ascertain whether the formulation process has reduced the relevant solvent levels to within acceptable amounts. A drug product should also be tested if a residual solvent is used during its manufacture.

See Appendix 2 for additional background information related to residual solvents.

CLASSIFICATION OF RESIDUAL SOLVENTS BY RISK ASSESSMENT

The term ‘‘tolerable daily intake’’ (TDI) is used by the International Program on Chemical Safety (IPCS) to describe exposure limits of toxic chemicals and the term ‘‘acceptable daily intake’’ (ADI) is used by the World Health Organization (WHO) and other national and international health authorities and institutes. The term ‘‘permitted daily exposure’’ (PDE) is defined as a pharmaceutically acceptable intake of residual solvents to avoid confusion of differing values for ADIs of the same substance.

Residual solvents specified in this General Chapter are listed in Appendix 1 by common names and structures. They were evaluated for their possible risk to human health and placed into one of three classes as follows:

Class 1	Residual Solvents: Solvents to be Avoided Known human carcinogens. Strongly suspected human carcinogens. Environmental hazards.
Class 2	Residual Solvents: Solvents to be Limited Nongenotoxic animal carcinogens or possible causative agents of other irreversible toxicity, such as neurotoxicity or terato genicity. Solvents suspected of other significant but reversible toxicities.
Class 3	Residual Solvents: Solvents with Low Toxic Potential Solvents with low toxic potential to humans; no health-based exposure limit is needed. [NOTE—Class 3 residual solvents may have PDEs of up to 50 mg ormore per day.]*

* For residual solvents with PDEs of more than 50 mg per day, see the discussion in the section *Class 3* under *Limits of Residual Solvents*.

PROCEDURES FOR ESTABLISHING EXPOSURE LIMITS

The procedure used to establish permitted daily exposures for residual solvents is presented in Appendix 3.

OPTIONS FOR DETERMINING LEVELS OF CLASS 2 RESIDUAL SOLVENTS

Two options are available to determine levels of Class 2 residual solvents.

Option 1

The concentration limits in ppm stated in *Table 2* are used. They were calculated using equation (1) below by assuming a product weight of 10 g administered daily.

$$\text{Concentration (ppm)} = \frac{1000 \times \text{PDE}}{\text{dose}} \quad (1)$$

Here, PDE is given in terms of mg per day, and dose is given in g per day.

These limits are considered acceptable for all drug substances, excipients, and drug products. Therefore, this option may be applied if the daily dose is not known or fixed. If all drug substances and excipients in a formulation meet the limits given in *Option 1*, these components may be used in any proportion. No further calculation is necessary provided the daily dose does not exceed 10 g. Products that are administered in doses greater than 10 g per day are to be considered under *Option 2*.

Option 2

It is not necessary for each component of the drug product to comply with the limits given in *Option 1*. The PDE in terms of mg per day as stated in *Table 2* can be used with the known maximum daily dose and equation (1) above to determine the concentration of residual solvent allowed in a drug product. Such limits are considered acceptable provided that it has been demonstrated that the residual solvent has been reduced to the practical minimum. The limits should be realistic in relation to analytical precision, manufacturing capability, and reasonable variation in the manufacturing process. The limits should also reflect contemporary manufacturing standards.

Option 2 may be applied by adding the amounts of a residual solvent present in each of the components of the drug product. The sum of the amounts of solvent per day should be less than that given by the PDE.

Consider an example of the application of *Option l* and *Option 2* to acetonitrile concentration in a drug product. The permitted daily exposure to acetonitrile is 4.1 mg per day; thus, the *Option 1* limit is 410 ppm. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	400	0.36
Excipient 2	3.8	800	3.04
Drug product	5.0	728	3.64

Excipient l meets the *Option l* limit, but the drug substance, excipient 2, and drug product do not meet the *Option l* limit. Nevertheless, the drug product meets the *Option 2* limit of 4.l mg per day and thus conforms to the acceptance criteria in this General Chapter.

Consider another example using acetonitrile as the residual solvent. The maximum administered daily weight of a drug product is 5.0 g, and the drug product contains two excipients. The composition of the drug product and the calculated maximum content of residual acetonitrile are given in the following table.

Component	Amount in Formulation (g)	Acetonitrile Content (ppm)	Daily Exposure (mg)
Drug substance	0.3	800	0.24
Excipient 1	0.9	2000	1.80
Excipient 2	3.8	800	3.04
Drug product	5.0	1016	5.08

In this example, the drug product meets neither the *Option 1* nor the *Option 2* limit. The manufacturer could test the drug product to determine if the formulation process reduced the level of acetonitrile. If the level of acetonitrile was not reduced to the allowed limit during formulation, the product fails the requirements of the test.

LIMITS OF RESIDUAL SOLVENTS

Ethylene Oxide

[NOTE—The test for ethylene oxide is conducted only where specified in the individual monograph.] The standard solution parameters and the procedure for determination are described in the individual monograph. Unless otherwise specified in the individual monograph, the limit is 10 µg per g.

Class 1

Class 1 residual solvents (*Table 1*) should not be employed in the manufacture of drug substances, excipients, and drug products because of the unacceptable toxicities or deleterious environmental effects of these residual solvents. However, if Class 1 residual solvents are used, their levels should be restricted as shown in *Table 1*, unless otherwise stated in the individual monograph. The solvent 1,1,1-

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trichloroethane is included in *Table 1* because it is an environmental hazard. The stated limit of 1500 ppm is based on safety data.

When Class 1 residual solvents are used in the manufacture of a drugsubstance, excipient, or drug product, the methodology described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter is to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for inclusion in the relevant individual monograph.

Table 1. Class 1 Residual Solvents

Solvent	Concentration Limit (ppm)	Concern
Benzene	2	Carcinogen
Carbon tetrachloride	4	Toxic and environmental hazard
1,2-Dichloroethane	5	Toxic
1,1-Dichloroethene	8	Toxic
1,1,1-Trichloroethane	1500	Environmental hazard

Class 2

Class 2 residual solvents (*Table 2*) should be limited in drug substances, excipients, and drug products because of the inherent toxicities of these residual solvents. PDEs are given to the nearest 0.1 mg per day, and concentrations are given to the nearest 10 ppm. The stated values do not reflect the necessary analytical precision of the determination procedure. Precision should be determined as part of the procedure validation.

If Class 2 residual solvents are present at greater than their *Option 1* limits, they should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for inclusion in the relevant individual monograph.

NOTE—The following Class 2 residual solvents are not readily detected by the headspace injection conditions described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter: formamide, 2-ethoxyethanol, 2-methoxyethanol, ethylene glycol, *N*-methylpyrrolidone, and sulfolane. Other appropriate validated procedures are to be employed for the control of these residual solvents. Such procedures shall be submitted to the USP for inclusion in the relevant individual monograph.

Table 2. Class 2 Residual Solvents

Solvent	PDE (mg/day)	Concentration limit (ppm)
Acetonitrile	4.1	410
Chlorobenzene	3.6	360
Chloroform	0.6	60
Cyclohexane	38.8	3880
1,2-Dichloroethene	18.7	1870
Dichloromethane	6.0	600
1,2-Dimethoxyethane	1.0	100
N,*N*-Dimethylacetamide	10.9	1090
N,*N*-Dimethylformamide	8.8	880
1,4-Dioxane	3.8	380
2-Ethoxyethanol	1.6	160
Ethylene glycol	6.2	620
Formamide	2.2	220

Solvent	PDE (mg/day)	Concentration limit (ppm)
Hexane	2.9	290
Methanol	30.0	3000
2-Methoxyethanol	0.5	50
Methylbutylketone	0.5	50
Methylcyclohexane	11.8	1180
N-Methylpyrrolidone	5.3	530
Nitromethane	0.5	50
Pyridine	2.0	200
Sulfolane	1.6	160
Tetrahydrofuran	7.2	720
Tetralin	1.0	100
Toluene	8.9	890
1,1,2-Trichloroethene	0.8	80
Xylene*	21.7	2170

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene

Class 3

Class 3 residual solvents (*Table 3*) may be regarded as less toxic and of lower risk to human health than Class 1 and Class 2 residual solvents. Class 3 includes no solvent known as a human health hazard at levels normally accepted in pharmaceuticals. However, there are no long-term toxicity or carcinogenicity studies for many of the residual solvents in Class 3. Available data indicate that they are less toxic in acute or short-term studies and negative in genotoxicity studies.

Unless otherwise stated in the individual monograph, Class 3 residual solvents are limited to not more than 50 mg per day (corresponding to 5000 ppm or 0.5% under *Option l*). If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day, that residual solvent should be identified and quantified. The procedures described in the *Identification, Control, and Quantification of Residual Solvents* section of this General Chapter are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for inclusion in the relevant individual monograph.

Table 3. Class 3 Residual Solvents

(limited by GMP or other quality-based requirements in drug substances, excipients, and drug products)

Acetic acid	Heptane
Acetone	Isobutyl acetate
Anisole	Isopropyl acetate
1-Butanol	Methyl acetate
2-Butanol	3-Methyl-1-butanol
Butyl acetate	Methylethylketone
tert-Butylmethyl ether	Methylisobutylketone
Cumene	2-Methyl-l-propanol
Dimethyl sulfoxide	Pentane
Ethanol	1-Pentanol
Ethyl acetate	1-Propanol
Ethyl ether	2-Propanol
Ethyl formate	Propyl acetate
Formic acid	

Other Residual Solvents

The residual solvents listed in *Table 4* may also be of interest to manufacturers of drug substances, excipients, or drug products. However, no adequate toxicological data on which to base a PDE was found. Specifications for these residual solvents will be provided in the respective individual monograph.

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Table 4. Other Residual Solvents

(for which no adequate toxicological data was found)

1,1-Diethoxypropane	Methyl isopropyl ketone
1,1-Dimethoxymethane	Methyltetrahydrofuran
2,2-Dimethoxypropane	Solvent Hexane
Isooctane	Trichloroacetic acid
Isopropyl ether	Trifluoroacetic acid

IDENTIFICATION, CONTROL, AND QUANTIFICATION OF RESIDUAL SOLVENTS

NOTE—The organic-free water specified in the following procedures produces no significantly interfering peaks when chromatographed.

Class 1 and Class 2 Residual Solvents

WATER-SOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution—Transfer 1.0 mL of USP Class 1 Residual Solvents Mixture RS to a 100-mL volumetric flask, add 9 mL of dimethyl sulfoxide, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 10-mL volumetric flask, dilute with water to volume, and mix.

Class 1 Standard Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriateheadspace vial, add 5.0 mL of water, apply stopper, cap, and mix.

Class 2 Standard Stock Solution—Transfer 1.0 mL of USP Class 2 Residual Solvents Mixture RS to a 100-mL volumetric flask, dilute with water to volume, and mix.

Class 2 Standard Solution—Transfer 1.0 mL of *Class 2 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of water, apply stopper, cap, and mix.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Test Solution—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, apply stopper, and cap.

Class 1 System Suitability Solution—Transfer 1.0 mL of *Class 1 Standard Stock Solution* to an appropriate headspace vial, add 5.0 mL of *Test Stock Solution*, apply stopper, cap, and mix.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1:5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, *Class 1 System Suitability Solution*, and *Class 2 Standard Solution*, and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in the table below) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, *Class 2 Standard Solution*, and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak re-

sponse of any peak in the *Test Solution* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or the *Class 2 Standard Solution*, proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Table 5. Headspace Operating Parameters

	Headspace Operating Parameter Sets		
	1	2	3
Equilibration temperature (°)	80	105	80
Equilibration time (min.)	60	45	45
Transfer-line temperature (°)	85	110	105
Carrier gas: nitrogen or helium at an appropriate pressure			
Pressurization time (s)	30	30	30
Injection volume (mL)	1	1	1

Procedure B—

Class 1 Standard Stock Solution, *Class 1 Standard Solution*, *Class 2 Standard Stock Solution*, *Class 2 Standard Solution*, *Test Stock Solution*, *Test Solution*, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 0.25-µm layer of phase G16, or a 0.53-mm × 30-m wide-bore column coated with a 0.25-µm layer of phase G16. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second and a split ratio of 1:5. The column temperature is maintained at 50° for 20 minutes, then raised at a rate of 6° per minute to 165°, and maintained at 165° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, the *Class 1 System Suitability Solution*, and the *Class 2 Standard Solution*, and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of benzene in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; the resolution, *R*, between acetonitrile and trichloroethylene in the *Class 2 Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameter sets described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, the *Class 2 Standard Solution*, and the *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in the *Test Solution* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or the *Class 2 Standard Solution*, proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Solution, *Class 2 Standard Solution*, *Test Stock Solution*, *Test Solution*, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A.*

Standard Solution—Transfer an accurately measured volume of the USP Reference Standard for each peak identified and verified by *Procedures A* and *B* to a suitable container, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a final concentration of 1/100 of the value stated in *Table 1* or *2* (under *Concentration limit*). Transfer 5.0 mL of this solution to an appropriate headspace vial, apply stopper, and cap.

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Chromatographic System (see *Chromatography* ⟨621⟩)—[NOTE—If the results of the chromatography from *Procedure A* are found to be inferior to those found with *Procedure B*, the *Chromatographic System* from *Procedure B* may be substituted.] The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica column coated with a 1.8-µm layer of phase G43 or a 0.53-mm × 30-m wide-bore column coated with a 3.0-µm layer of phase G43. The carrier gas is nitrogen or helium with a linear velocity of about 35 cm per second, and a split ratio of 1:5. The column temperature is maintained at 40° for 20 minutes, then raised at a rate of 10° per minute to 240°, and maintained at 240° for 20 minutes. The injection port and detector temperatures are maintained at 140° and 250°, respectively. Chromatograph the *Class 1 Standard Solution*, the *Class 1 System Suitability Solution*, and the *Class 2 Standard Solution*, and record the peak responses as directed for *Procedure:* the signal-to-noise ratio of 1,1,1-trichloroethane in the *Class 1 Standard Solution* is not less than 5; the signal-to-noise ratio of each peak in the *Class 1 System Suitability Solution* is not less than 3; and the resolution, *R*, between acetonitrile and methylene chloride in the *Class 2 Standard Solution* is not less than 1.0.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution* and *Test Solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$4(C/W)(r_U/r_S),$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_S are the peak responses of each residual solvent obtained from the *Test Solution* and the *Standard Solution*, respectively.

WATER-INSOLUBLE ARTICLES

Procedure A—

Class 1 Standard Stock Solution, *Class 1 Standard Solution*, *Class 1 System Suitability Solution*, *Class 2 Standard Stock Solution*, *Class 2 Standard Solution*, and *Chromatographic System*—Proceed as directed for *Procedure A* under *Water-Soluble Articles*.

Test Stock Solution—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

Test Solution 1—Transfer 5.0 mL of *Test Stock Solution* to an appropriate headspace vial, add 1.0 mL of dimethylformamide, apply stopper, cap, and mix.

Test Solution 2—Transfer about 250 mg of the article under test, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with 1,3-dimethyl-2-imidazolidinone to volume, and mix. Transfer 5.0 mL of this solution to an appropriate headspace vial, add 1.0 mL of 1,3-dimethyl-2-imidazolidinone, apply stopper, cap, and mix.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, the *Class 2 Standard Solution*, *Test Solution 1*, and *Test Solution 2* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If a peak response of any peak in *Test Solution 1* is greater than or equal to a corresponding peak in either the *Class 1 Standard Solution* or the *Class 2 Standard Solution,* proceed to *Procedure B* to verify the identity of the peak; otherwise the

article meets the requirements of this test. If the peak response for dimethylformamide or *N*,*N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Standard Solution*, proceed to *Procedure B* to verify the identity of the peak; otherwise the article meets the requirements of this test.

Procedure B—

Class 1 Standard Stock Solution, *Class 1 Standard Solution*, *Class 2 Standard Stock Solution*, *Class 2 Standard Solution*, and *Class 1 System Suitability Solution*—Prepare as directed for *Procedure A* under *Water-Soluble Articles*.

Test Stock Solution, Test Solution 1, and *Test Solution 2*—Proceed as directed for *Procedure A*.

Chromatographic System—Proceed as directed for *Procedure B* under *Water-Soluble Articles*.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Class 1 Standard Solution*, *Class 2 Standard Solution*, *Test Solution 1*, and/or *Test Solution 2* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. If the peak response(s) in *Test Solution 1* of the peak(s) identified in *Procedure A* is/are greater than or equal to a corresponding peak(s) in either the *Class 1 Standard Solution* or the *Class 2 Standard Solution*, proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test. If the peak response for dimethylformamide or *N*,*N*-dimethylacetamide in *Test Solution 2* is greater than or equal to the corresponding peak in the *Class 2 Standard Solution*, proceed to *Procedure C* to quantify the peak; otherwise the article meets the requirements of this test.

Procedure C—

Class 1 Standard Solution, *Class 1 System Suitability Solution*, and *Class 2 Standard Solution*—Proceed as directed for *Procedure A* under *Water-Soluble Articles*.

Test Stock Solution, *Test Solution 1*, and *Test Solution 2*—Proceed as directed for *Procedure A*.

Standard Solution, and *Chromatographic System*—Proceed as directed for *Procedure C* under *Water-Soluble Articles*.

Procedure—Separately inject (following one of the headspace operating parameters described in *Table 5*) equal volumes of headspace (about 1.0 mL) of the *Standard Solution*, *Test Solution 1*, and/or *Test Solution 2* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount, in ppm, of each residual solvent found in the article under test by the formula:

$$4(C/W)(r_U/r_S),$$

in which C is the concentration, in ppm, of the appropriate USP Reference Standard in the *Standard Solution; W* is the weight, in g, of the article under test taken to prepare the *Test Stock Solution;* and r_U and r_S are the peak responses of each residual solvent obtained from *Test Solution 1* or *Test Solution 2* and the *Standard Solution*, respectively.

Class 3 Residual Solvents

If only Class 3 solvents are present, the level of residual solvents is to be determined as directed under *Loss on Drying* ⟨731⟩. If the loss on drying value is greater than 0.5%, a water determination should be performedon the test sample as directed under *Water Determination* ⟨921⟩. Determine the water by *Method Ia*, unless otherwise specified in the individual monograph. If a Class 3 solvent limit in an individual monograph is greater than 50 mg per day (corre-

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sponding to 5000 ppm or 0.5% under *Option l*), that residual solvent should be identified and quantified, and the procedures as described above are to be applied wherever possible. Otherwise an appropriate validated procedure is to be employed. Such procedure shall be submitted to the USP for inclusion in the relevant individual monograph. A flow diagram for the application of residual solvent limit tests is shown in *Figure 1*.

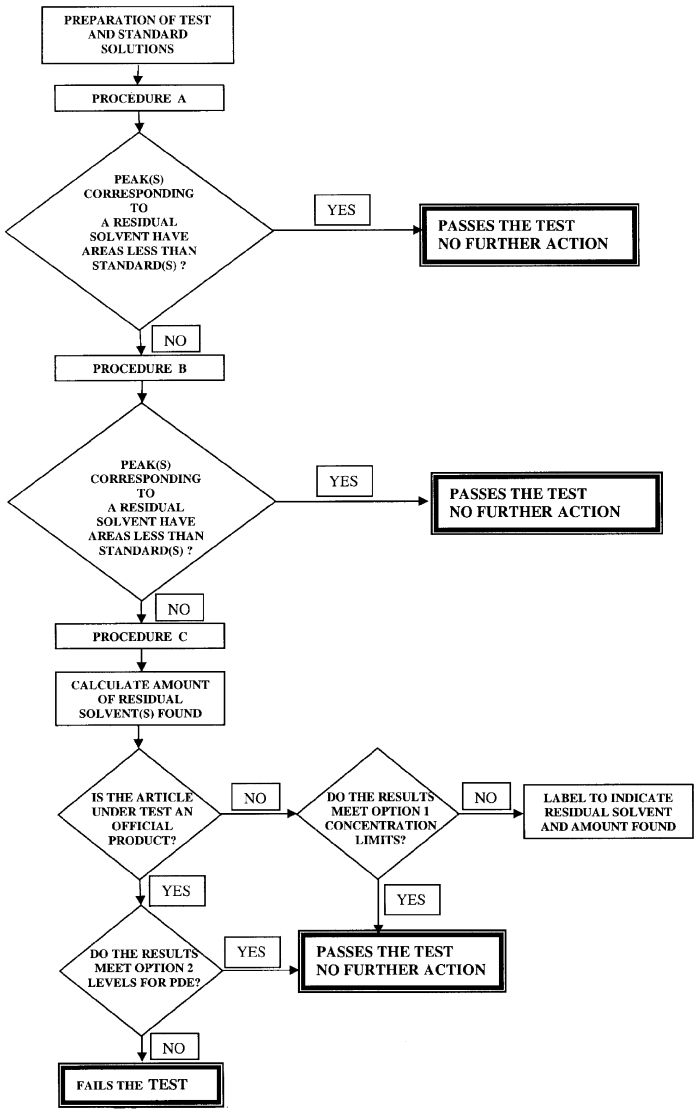

Fig. 1. Diagram relating to the identification of residual solvents and the application of limit tests.

OTHER ANALYTICAL PROCEDURES

The following procedures, with any necessary variations, are used where specified in the individual monographs.

Method I

A gas chromatograph capable of temperature programming and equipped with a wide-bore, wall-coated open tubular column and a flame-ionization detector is used in the following procedure.

Standard Solution—Prepare a solution, in organic-free water, or the solvent specified in the monograph, containing in each mL, 12.0 µg of methylene chloride, 7.6 µg of 1,4-dioxane, 1.6 µg of trichloroethylene, and 1.2 µg of chloroform. [NOTE—Prepare fresh daily.]

Test Solution—Dissolve in organic-free water, or the solvent specified in the monograph, an accurately weighed portion of the material to be tested to obtain a final solution having a known concentration of about 20 mg of the test material per mL.

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused silica analytical column coated with a 5-µm chemically cross-linked G27 stationary phase and a 0.53-mm × 5-m silica guard column deactivated with phenylmethyl siloxane. The carrier gas is helium with a linear velocity of about 35 cm per second. [NOTE—When a makeup gas is used, nitrogen is recommended.] The injection port temperature and the detector temperature are maintained at 70° and 260°, respectively. The column temperature is programmed as follows. Initially, the column temperature is maintained at 35° for 5 minutes, then increased at a rate of 8° per minute to 175°, followed by an increase at a rate of 35° per minute to 260°, and maintained at 260° for at least 16 minutes.

Inject the *Standard Solution*, and record the peak responses as directed for *Procedure:* a suitable system is one that yields chromatograms in which all of the components in the *Standard Solution* are resolved; the resolution, *R*, between any two components is not less than 1.0; and the relative standard deviation of the individual peak responses from replicate injections is not more than 15%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard Solution* and the *Test Solution* into the chromatograph, record the chromatograms, and measure the peak responses.

Identify, on the basis of retention time, any peaks present in the chromatogram of the *Test Solution*. The identity and peak response in the chromatogram may be established as being from any of the organic volatile impurities listed in the table shown below or from some other volatile impurity eluting with a comparable retention time as determined by mass spectrometric relative abundance procedures or by the use of a second validated column containing a different stationary phase.

Unless otherwise specified in the individual monograph, the amount of each organic volatile impurity present in the material does not exceed the limit given in the table shown below.

Organic Volatile Impurity	Limit (µg per g)
Chloroform	60
1,4-Dioxane	380
Methylene Chloride	600
Trichloroethylene	80

Method IV

Standard Solution—Prepare as directed for *Standard Solution* in *Method I.* Pipet 5 mL of the solution into a vial fitted with a septum and crimp cap, containing 1 g of anhydrous sodium sulfate, and seal. Heat the sealed vial at 80° for 60 minutes.

Test Solution—Transfer 100 mg, accurately weighed, of the material under test to a vial, add 5.0 mL of water, or the solvent specified in the monograph, and 1 g of anhydrous

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sodium sulfate, and seal with a septum and crimp cap. Heat the sealed vial at 80° for 60 minutes, or as specified in the individual monograph.

Chromatographic System and **Procedure**—[NOTE—The use of headspace apparatuses that automatically transfer a measured amount of headspace is allowed. Also, the use of a guard column in this headspace procedure is not necessary.] Proceed as directed for *Method V*, except to inject, using a heated gas-tight syringe, 1 mL of the headspace.

Method V

Standard Solution and **Test Solution**—Prepare as directed for *Method I*.

Chromatographic System (see *Chromatography* ⟨621⟩)— The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused silica analytical column coated with a 3.0-µm G43 stationary phase, and a 0.53-mm × 5-m silica guard column deactivated with phenylmethyl siloxane. The carrier gas is helium with a linear velocity of about 35 cm per second. The injection port and detector temperatures are maintained at 140° and 260°, respectively. The column temperature is programmed according to the following steps. It is maintained at 40° for 20 minutes, then increased rapidly to 240°, and maintained at 240° for 20 minutes.

Inject the *Standard Solution*, and record the peak responses as directed for *Procedure:* a suitable system is one that yields chromatograms in which all of the components in the *Standard Solution* are resolved; the resolution, *R*, between any two components is not less than 3; and the relative standard deviation of the individual peak responses from replicate injections is not more than 15%.

Procedure—Proceed as directed for *Method I*, the injection volume being about 1 µL.

Method VI

Standard Solution and **Test Solution**—Prepare as directed for *Method I.*

Chromatographic System (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector. The column and column temperature conditions, as chosen from the list below (see *Table 6*), are specified in the individual monograph. The carrier gas, linear velocity or flow rate, and detector and injector temperatures are appropriate to the column dimensions and column temperatures chosen from the list below.

Inject the *Standard Solution*, and record the peak responses as directed for *Procedure:* a suitable system is one that yields the chromatograms in which all of the components in the *Standard Solution* are resolved; the resolution, *R*, between any two components is not less than 1.0; and the relative standard deviation of the individual peak responses from replicate injections is not more than 15%.

Procedure—Proceed as directed for *Method I*, the injection volume being about 1 µL.

Table 6. Chromatographic Conditions for Method VI

Chromatographic Conditions	USP Column Designation	Column Size	Column Temperature
A	S3	3-mm × 2-m	190°
B	S2	3-mm × 2.1-m	160°
C	G16	0.53-mm × 30-m	40°
D	G39	3-mm × 2-m	65°
E	G16	3-mm × 2-m	70°
F	S4	2-mm × 2.5-m	Hold 120° (35 min.) Gradient 120°–200°(2°/min.) Hold 20 min.
H	G14	2-mm × 2.5-m	Hold 45° (3 min.) Gradient 45°–120° (8°/min.) Hold 15 min.
I	G27	0.53-mm × 30-m	Hold 35° (5 min.) 35°–175° (8° /min.) 175°–260°(35°/min.) Hold 16 min.
J	G16	0.33-mm × 30-m	Hold 50° (20 min.) 50°–165° (6°/min.) Hold 20 min.

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GLOSSARY

Genotoxic carcinogens: Carcinogens that produce cancer by affecting genes or chromosomes.

Lowest-observed-effect level (LOEL): The lowest dose of a substance in a study or group of studies that produces biologically significant increases in frequency or severity of any effects in exposed humans or animals.

Modifying factor: A factor determined by professional judgment of a toxicologist and applied to bioassay data so that the data can be safely related to humans.

Neurotoxicity: The ability of a substance to cause adverse effects on the nervous system.

No-observed-effect level (NOEL): The highest dose of a substance at which there are no biologically significant increases in frequency or severity of any effects in exposed humans or animals.

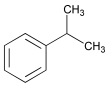
Permitted daily exposure (PDE): The maximum acceptable intake per day of a residual solvent in pharmaceutical products.

Reversible toxicity: The occurrence of harmful effects that are caused by a substance and that disappear after exposure to the substance ends.

Strongly suspected human carcinogen: A substance for which there is no epidemiological evidence of carcinogenesis but for which there are positive genotoxicity data and clear evidence of carcinogenesis in rodents.

Teratogenicity: The occurrence of structural malformations in a developing fetus when a substance is administered during pregnancy.

APPENDIX 1. LIST OF RESIDUAL SOLVENTS INCLUDED IN THIS GENERAL CHAPTER

Solvent	Other Names	Structure	Class
Acetic acid	Ethanoic acid	CH_3COOH	Class 3
Acetone	2-Propanone Propan-2-one	CH_3COCH_3	Class 3
Acetonitrile		CH_3CN	Class 2
Anisole	Methoxybenzene		Class 3
Benzene	Benzol		Class 1
1-Butanol	*n*-Butyl alcohol Butan-1-ol	$CH_3(CH_2)_3OH$	Class 3
2-Butanol	*sec*-Butyl alcohol Butan-2-ol	$CH_3CH_2CH(OH)CH_3$	Class 3
Butyl acetate	Acetic acid butyl ester	$CH_3COO(CH_2)_3CH_3$	Class 3
tert-Butylmethyl ether	2-Methoxy-2-methylpropane	$(CH_3)_3COCH_3$	Class 3
Carbon tetrachloride	Tetrachloromethane	CCl_4	Class 1
Chlorobenzene			Class 2
Chloroform	Trichloromethane	$CHCl_3$	Class 2
Cumene	Isopropylbenzene (1-Methylethyl)benzene		Class 3

Solvent	Other Names	Structure	Class
Cyclohexane	Hexamethylene		Class 2
1,2-Dichloroethane	*sym*-Dichloroethane Ethylene dichloride Ethylene chloride	CH_2ClCH_2Cl	Class 1
1,1-Dichloroethene	1,1-Dichloroethylene Vinylidene chloride	$H_2C{=}CCl_2$	Class 1
1,2-Dichloroethene	1,2-Dichloroethylene Acetylene dichloride	$ClHC{=}CHCl$	Class 2
Dichloromethane	Methylene chloride	CH_2Cl_2	Class 2
1,2-Dimethoxyethane	Ethyleneglycol dimethyl ether Monoglyme Dimethyl cellosolve	$H_3COCH_2CH_2OCH_3$	Class 2
N,*N*-Dimethylacetamide	DMA	$CH_3CON(CH_3)_2$	Class 2
N,*N*-Dimethylformamide	DMF	$HCON(CH_3)_2$	Class 2
Dimethyl sulfoxide	Methylsulfinylmethane Methyl sulfoxide DMSO	$(CH_3)_2SO$	Class 3
1,4-Dioxane	*p*-Dioxane [1,4]Dioxane		Class 2
Ethanol	Ethyl alcohol	CH_3CH_2OH	Class 3
2-Ethoxyethanol	Cellosolve	$CH_3CH_2OCH_2CH_2OH$	Class 2
Ethyl acetate	Acetic acid ethyl ester	$CH_3COOCH_2CH_3$	Class 3
Ethylene glycol	1,2-Dihydroxyethane 1,2-Ethanediol	$HOCH_2CH_2OH$	Class 2
Ethyl ether	Diethyl ether Ethoxyethane 1,1′-Oxybisethane	$CH_3CH_2OCH_2CH_3$	Class 3
Ethyl formate	Formic acid ethyl ester	$HCOOCH_2CH_3$	Class 3
Formamide	Methanamide	$HCONH_2$	Class 2
Formic acid		HCOOH	Class 3

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Solvent	Other Names	Structure	Class
Heptane	*n*-Heptane	$CH_3(CH_2)_5CH_3$	Class 3
Hexane	*n*-Hexane	$CH_3(CH_2)_4CH_3$	Class 2
Isobutyl acetate	Acetic acid isobutyl ester	$CH_3COOCH_2CH(CH_3)_2$	Class 3
Isopropyl acetate	Acetic acid isopropyl ester	$CH_3COOCH(CH_3)_2$	Class 3
Methanol	Methyl alcohol	CH_3OH	Class 2
2-Methoxyethanol	Methyl cellosolve	$CH_3OCH_2CH_2OH$	Class 2
Methyl acetate	Acetic acid methyl ester	CH_3COOCH_3	Class 3
3-Methyl-1-butanol	Isoamyl alcohol Isopentyl alcohol 3-Methylbutan-1-ol	$(CH_3)_2CHCH_2CH_2OH$	Class 3
Methylbutylketone	2-Hexanone Hexan-2-one	$CH_3(CH_2)_3COCH_3$	Class 2
Methylcyclohexane	Cyclohexylmethane		Class 2
Methylethylketone	2-Butanone MEK Butan-2-one	$CH_3CH_2COCH_3$	Class 3
Methyl isobutyl ketone	4-Methylpentan-2-one 4-Methyl-2-pentanone MIBK	$CH_3COCH_2CH(CH_3)_2$	Class 3
2-Methyl-1-propanol	Isobutyl alcohol 2-Methylpropan-1-ol	$(CH_3)_2CHCH_2OH$	Class 3
N-Methylpyrrolidone	1-Methylpyrrolidin-2-one 1-Methyl-2-pyrrolidinone		Class 2
Nitromethane		CH_3NO_2	Class 2
Pentane	*n*-Pentane	$CH_3(CH_2)_3CH_3$	Class 3
1-Pentanol	Amyl alcohol Pentan-1-ol Pentyl alcohol	$CH_3(CH_2)_3CH_2OH$	Class 3
1-Propanol	Propan-1-ol Propyl alcohol	$CH_3CH_2CH_2OH$	Class 3

Solvent	Other Names	Structure	Class
2-Propanol	Propan-2-ol Isopropyl alcohol	$(CH_3)_2CHOH$	Class 3
Propyl acetate	Acetic acid propyl ester	$CH_3COOCH_2CH_2CH_3$	Class 3
Pyridine			Class 2
Sulfolane	Tetrahydrothiophene 1,1-dioxide		Class 2
Tetrahydrofuran	Tetramethylene oxide Oxacyclopentane		Class 2
Tetralin	1,2,3,4-Tetrahydronaphthalene		Class 2
Toluene	Methylbenzene		Class 2
1,1,1-Trichloroethane	Methylchloroform	CH_3CCl_3	Class 1
1,1,2-Trichloroethene	Trichloroethene	$HClC{=}CCl_2$	Class 2
Xylene*	Dimethybenzene Xylol		Class 2

* Usually 60% *m*-xylene, 14% *p*-xylene, 9% *o*-xylene with 17% ethyl benzene.

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APPENDIX 2. ADDITIONAL BACKGROUND

A2.1. Environmental Regulation of Organic Volatile Solvents

Several of the residual solvents frequently used in the production of pharmaceuticals are listed as toxic chemicals in Environmental Health Criteria (EHC) monographs and in the Integrated Risk Information System (IRIS). The objectives of such groups as the International Programme on Chemical Safety (IPCS), the United States Environmental Protection Agency (EPA), and the United States Food and Drug Administration (FDA), include the determination of acceptable exposure levels. The goal is maintenance of en-

vironmental integrity and protection of human health against the possible deleterious effects of chemicals resulting from long-term environmental exposure. The procedures involved in the estimation of maximum safe exposure limits are usually based on long-term studies. When long-term study data are unavailable, shorter term study data can be used with modification of the approach, such as use of larger safety factors. The approach described therein relates primarily to long-term or lifetime exposure of the general population in the ambient environment (i.e., ambient air, food, drinking water, and other media).

A2.2. Residual Solvents in Pharmaceuticals

Exposure limits in this General Chapter are established by referring to methodologies and toxicity data described in EHC and IRIS monographs. However, the following specific assumptions about residual solvents to be used in the synthesis and formulation of pharmaceutical products should be taken into account in establishing exposure limits.

1. Patients (not the general population) use pharmaceuticals to treat their diseases or for prophylaxis to prevent infection or disease.
2. The assumption of lifetime patient exposure is not necessary for most pharmaceutical products but may be appropriate as a working hypothesis to reduce risk to human health.
3. Residual solvents are unavoidable components in pharmaceutical production and will often be a part of medicinal products.
4. Residual solvents should not exceed recommended levels except in exceptional circumstances.
5. Data from toxicological studies that are used to determine acceptable levels for residual solvents should have been generated using appropriate protocols such as those described, for example, by the Organization for Economic Cooperation and Development (OECD), EPA, and the FDA Red Book.

APPENDIX 3. PROCEDURES FOR ESTABLISHING EXPOSURE LIMITS

The Gaylor-Kodell method of risk assessment (Gaylor, D. W. and Kodell, R. L. Linear Interpolation Algorithm for Low Dose Assessment of Toxic Substance. *Journal of Environmental Pathology and Toxicology*, 4:305, 1980) is appropriate for Class 1 carcinogenic solvents. Only in cases where reliable carcinogenicity data are available should extrapolation by the use of mathematical models be applied to setting exposure limits. Exposure limits for Class 1 residual solvents could be determined with the use of a large safety factor (i.e., 10,000 to 100,000) with respect to the no-observed-effect level (NOEL). Detection and quantification of these residual solvents should be performed by state-of-the-art analytical techniques.

Acceptable exposure levels in this General Chapter for Class 2 residual solvents were established by calculation of PDE values according to the procedures for setting exposure limits in pharmaceuticals (page 5748 of *Pharmacopeial Forum* 15(6) [Nov.–Dec. 1989]), and the method adopted by IPCS for Assessing Human Health Risk of Chemicals (*Environmental Health Criteria 170*, WHO, 1994). These procedures are similar to those used by the U.S. EPA (IRIS) and the U.S. FDA (*Red Book*) and others. The method is outlined here to give a better understanding of the origin of the PDE values. It is not necessary to perform these calculations in order to use the PDE values presented in *Table 2* of this document.

PDE is derived from the no-observed-effect level (NOEL), or the lowest-observed effect level (LOEL), in the most relevant animal study as follows:

$$\text{PDE} = \frac{\text{NOEL} \times \text{Weight Adjustment}}{\text{F1} \times \text{F2} \times \text{F3} \times \text{F4} \times \text{F5}} \quad (1)$$

The PDE is derived preferably from a NOEL. If no NOEL is obtained, the LOEL may be used. Modifying factors proposed here, for relating the data to humans, are the same kind of "uncertainty factors" used in Environmental Health Criteria (*Environmental Health Criteria* 170, WHO, Geneva, 1994) and "modifying factors" or "safety factors" in *Pharmacopeial Forum*. The assumption of 100 percent systemic exposure is used in all calculations regardless of route of administration.

The modifying factors are as follows:

F1 = A factor to account for extrapolation between species

- F1 = 2 for extrapolation from dogs to humans
- F1 = 2.5 for extrapolation from rabbits to humans
- F1 = 3 for extrapolation from monkeys to humans
- F1 = 5 for extrapolation from rats to humans
- F1 = 10 for extrapolation from other animals to humans
- F1 = 12 for extrapolation from mice to humans

F1 takes into account the comparative surface area to body weight ratios for the species concerned and for man. Surface area (S) is calculated as:

$$S = kM^{0.67}, \quad (2)$$

in which M = body weight, and the constant k has been taken to be 10. The body weights used in the equation are those shown below in *Table A3.-1*.

F2 = A factor of 10 to account for variability between individuals. A factor of 10 is generally given for all organic solvents, and 10 is used consistently in this General Chapter.

F3 = A variable factor to account for toxicity studies of short-term exposure.

- F3 = 1 for studies that last at least one half-lifetime (1 year for rodents or rabbits; 7 years for cats, dogs and monkeys).
- F3 = 1 for reproductive studies in which the whole period of organogenesis is covered.
- F3 = 2 for a 6-month study in rodents, or a 3.5-year study in nonrodents.
- F3 = 5 for a 3-month study in rodents, or a 2-year study in nonrodents.
- F3 = 10 for studies of a shorter duration.

In all cases, the higher factor has been used for study durations between the time points (e.g., a factor of 2 for a 9-month rodent study).

F4 = A factor that may be applied in cases of severe toxicity, e.g., nongenotoxic carcinogenicity, neurotoxicity, or teratogenicity. In studies of reproductive toxicity, the following factors are used:

- F4 = 1 for fetal toxicity associated with maternal toxicity
- F4 = 5 for fetal toxicity without maternal toxicity
- F4 = 5 for a teratogenic effect with maternal toxicity
- F4 = 10 for a teratogenic effect without maternal toxicity

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F5 = A variable factor that may be applied if the no-effect level was not established.

When only a LOEL is available, a factor of up to 10 can be used depending on the severity of the toxicity. The weight adjustment assumes an arbitrary adult human body weight for either sex of 50 kilograms (kg). This relatively low weight provides an additional safety factor against the standard weights of 60 kg or 70 kg that are often used in this type of calculation. It is recognized that some adult patients weigh less than 50 kg; these patients are considered to be accommodated by the built-in safety factors used to determine a PDE. If the solvent was present in a formulation specifically intended for pediatric use, an adjustment for a lower body weight would be appropriate.

As an example of the application of this equation, consider a toxicity study of acetonitrile in mice that is summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S24. The NOEL is calculated to be 50.7 mg kg^{-1} day^{-1}. The PDE for acetonitrile in this study is calculated as follows:

$$\text{PDE} = \frac{50.7\ \text{mg kg}^{-1}\ \text{day}^{-1} \times 50\ \text{kg}}{12 \times 10 \times 5 \times 1 \times 1} = 4.22\ \text{mg day}^{-1}$$

In this example,

F1 = 12 to account for the extrapolation from mice to humans

F2 = 10 to account for differences between individual humans

F3 = 5 because the duration of the study was only 13 weeks

F4 = 1 because no severe toxicity was encountered

F5 = 1 because the no-effect level was determined

A3.-1. - Values Used in the Calculations in This Document

Rat body weight	425 g
Pregnant rat body weight	330 g
Mouse body weight	28 g
Pregnant mouse body weight	30g
Guinea-pig body weight	500 g
Rhesus monkey body weight	2.5 kg
Rabbit body weight (pregnant or not)	4 kg
Beagle dog body weight	11.5 kg
Rat respiratory volume	290 L/day
Mouse respiratory volume	43 L/day
Rabbit respiratory volume	1440 L/day
Guinea-pig respiratory volume	430 L day
Human respiratory volume	28,800 L/day
Dog respiratory volume	9000 L/day
Monkey respiratory volume	1150 L/day
Mouse water consumption	5 mL/day
Rat water consumption	30 mL/day
Rat food consumption	30 g/day

The equation for an ideal gas, $PV = nRT$, is used to convert concentrations of gases used in inhalation studies from units of ppm to units of mg/L or mg/m^3. Consider as an example the rat reproductive toxicity study by inhalation of carbon tetrachloride (molecular weight 153.84) summarized in *Pharmeuropa*, Vol. 9, No. 1, Supplement, April 1997, page S9.

$$\frac{n}{V} = \frac{P}{RT} = \frac{300 \times 10^{-6}\ \text{atm} \times 153\ 840\ \text{mg mol}^{-1}}{0.082\ \text{L atm K}^{-1}\ \text{mol}^{-1} \times 298\ \text{K}} = \frac{46.15\ \text{mg}}{24.45\ \text{L}} = 1.89\ \text{mg/L}$$

The relationship 1000 liters = 1 m^3 is used to convert to mg/m^3.■1S (*USP27*)

BRIEFING

⟨601⟩ Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers, *USP 26* page 2105 and page 1470 of *PF* 28(5) [Sept.–Oct. 2002]. Dose uniformity of inhalation formulations is regulated in the general chapters *Aerosols, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩ and *Uniformity of Dosage Units* ⟨905⟩. The most recent revisions to these chapters (*PF* 28[5]) will be adopted in *USP 26*, *Supplement 2*. In that revision all delivered dose uniformity testing was placed in ⟨601⟩, leaving only the uniformity tests for premetered dosage units in ⟨905⟩. Clarifying changes were also made to the text on the subject of *Mass Balance* during cascade impaction testing.

In the present revision, the Aerosol Expert Committee has made five significant changes to the document.

(1) *Delivered-Dose Uniformity* testing for nasal sprays has been added and the chapter ⟨601⟩ title modified to *Aerosols*, *Nasal Sprays*, *Metered-Dose Inhalers*, *and Dry Powder Inhalers*. In the longer term, the committee intends to add further tests under the subheading *Nasal Sprays.*

(2) The term "target-delivered dose" has been introduced and defined for the purpose of metered-dose and dry powder inhaler testing. The Committee recommended that this "target-delivered dose", not the label claim, should be used as the mean, about which the variance of the delivered dose is determined and specified. This is especially important for dry powder inhalers, for which the label claim is often significantly greater than the delivered dose. In such cases, the "target-delivered dose" is both method- and inhaler-dependent. Thus, it should be defined using a specific method, by determining the average dose delivered across a large number of the inhalers in question, preferably sampled from a variety of production batches.

(3) A new instrument, the "Next Generation Pharmaceutical Impactor", and associated methods for its use, has been added to ⟨601⟩. This cascade impactor is for use when determining the aerodynamic size distributions of drug doses delivered from metered-dose and dry powder inhalers. However, to aid with the global regulation of these products, these new methods have been harmonized between the *European Pharmacopoeia* and the *USP.*

(4) All of the cascade impactor testing methodology has been modified to reflect the new awareness that particle re-entrainment often confounds the determination of aerodynamic size distributions from metered-dose and dry powder inhalers. According to USP, stage coating is now to be required when performing cascade impaction, unless it has been proven to be unnecessary.

(5) Finally, *Apparatus 4*, the multistage liquid impinger, has a small number of stages and is used extensively outside the USA. Because the USP is used in countries other than the United States, the Aerosol Expert Committee has chosen to leave the method in place for countries other than the USA.

Acceptance criteria for dose uniformity are currently a subject of much debate. A STAGE 4 draft in the harmonization process of ⟨905⟩ has been published (*PF* 27[3], page 2615) that contains specifications for inhalers and unit doses for use in inhalers, which the Aerosol Expert Committee expects to see changed. Thus, acceptance criteria are not addressed in the presently proposed revision although the committee retains a long-term goal of changing the statistical principle for determining dose uniformity. It is intended to address this issue for delivered-dose uniformity in future revisions of ⟨601⟩.

(AER: K. Zaidi) RTS—39975-1

Change to read:

⟨601⟩ AEROSOLS,

■NASAL SPRAYS,■1S (*USP27*) METERED-DOSE INHALERS, AND DRY POWDER INHALERS

This general chapter contains test methods for propellants, pressurized topical aerosols,

■nasal sprays,■1S (*USP27*)
metered-dose inhalers, and propellant-free dry powder inhalers used to aerosolize, or to aerosolize and meter, doses of powders for inhalation. Apply these methods, where indicated, in the testing of the appropriate dosage forms.

Change to read:

PROPELLANTS

Caution—Hydrocarbon propellants are highly flammable and explosive. Observe precautions, and perform sampling and analytical operations in a well-ventilated fume hood.

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General Sampling Procedure

This procedure is used to obtain test specimens for those propellants that occur as gases at about 25° and that are stored in pressurized cylinders. Use a stainless steel sample cylinder equipped with a stainless steel valve and having a capacity of not less than 200 mL and a pressure rating of 240 psi or more. Dry the cylinder with the valve open at 110° for 2 hours, and evacuate the hot cylinder to less than 1 mm of mercury. Close the valve, cool, and weigh. Connect one end of a charging line tightly to the propellant container and the other end loosely to the sample cylinder. Carefully open the propellant container, and allow the propellant to flush out the charging line through the loose connection. Avoid excessive flushing, which causes moisture to freeze in the charging line and connections. Tighten the fitting on the sample cylinder, and open the sample cylinder valve, allowing the propellant to flow into the evacuated cylinder. Continue sampling until the desired amount of specimen is obtained, then close the propellant container valve, and finally close the sample cylinder valve. [*Caution—Do not overload the sample cylinder; hydraulic expansion due to temperature change can cause overloaded cylinders to explode.*] Again weigh the charged sample cylinder, and calculate the weight of the specimen.

Approximate Boiling Temperature

Transfer a 100-mL specimen to a tared, pear-shaped, 100-mL centrifuge tube containing a few boiling stones, and weigh. Suspend a thermometer in the liquid, and place the tube in a medium maintained at a temperature of 32° above the expected boiling temperature. When the thermometer reading becomes constant, record as the boiling temperature the thermometer reading after

■at least■2S (*USP26*)
5% of the specimen has distilled. Retain the remainder of the specimen for the determination of *High-Boiling Residues*.

High-Boiling Residues, Method I

Allow 85 mL of the specimen to distil, as directed in the test for *Approximate Boiling Temperature*, and transfer the centrifuge tube containing the remaining 15 mL of specimen to a medium maintained at a temperature 10° above the boiling temperature. After 30 minutes, remove the tube from the water bath, blot dry, and weigh. Calculate the weight of the residue.

High-Boiling Residues, Method II

Prepare a cooling coil from copper tubing (about 6 mm outside diameter × about 6.1 m long) to fit into a vacuum-jacketed flask. Immerse the cooling coil in a mixture of dry ice and acetone in a vacuum-jacketed flask, and connect one end of the tubing to the propellant sample cylinder. Carefully open the sample cylinder valve, flush the cooling coil with about 50 mL of the propellant, and discard this portion of liquefied propellant. Continue delivering liquefied propellant from the cooling coil, and collect it in a previously chilled 1000-mL sedimentation cone until the cone is filled to the 1000-mL mark. Allow the propellant to evaporate, using a warm water bath maintained at about 40° to reduce evaporating time. When all of the liquid has evaporated, rinse the sedimentation cone with two 50-mL portions of pentane, and combine the rinsings in a tared 150-mL evaporating dish. Transfer 100 mL of the pentane solvent to a second tared 150-mL evaporating dish, place both evaporating dishes on a water bath, evaporate to dryness, and heat the dishes in an oven at 100° for 60 minutes. Cool the dishes in a desiccator, and weigh. Repeat the heating for 15-minute periods until successive weighings are within 0.1 mg, and calculate the weight of the residue obtained from the propellant as the difference between the weights of the residues in the two evaporating dishes.

Water Content

Proceed as directed under *Water Determination* ⟨921⟩, with the following modifications: (a) Provide the closed-system titrating vessel with an opening through which passes a coarse-porosity gas dispersion tube connected to a sampling cylinder. (b) Dilute the *Reagent* with anhydrous methanol to give a water equivalence factor of between 0.2 and 1.0 mg per mL; age this diluted solution for not less than 16 hours before standardization. (c) Obtain a 100-g specimen as directed under *General Sampling Procedure*, and introduce the specimen into the titration vessel through the gas dispersion tube at a rate of about 100 mL of gas per minute; if necessary, heat the sample cylinder gently to maintain this flow rate.

Other Determinations

For those aerosols that use propellants, perform the tests specified in the individual *NF* propellant monographs.

AEROSOLS

Because leaching of extractable substances into pressurized formulations should be minimized, valve materials and other components that are in contact with the product meet the requirements under *Elastomeric Closures for Injections* ⟨381⟩. [NOTE—Under *Physicochemical Test Procedures* in ⟨381⟩ the directions for preparing a sample require pre-extraction, which may cause an underestimate of the amount of extractables from a given component.] See also *Aerosols* under *Pharmaceutical Dosage Forms* ⟨1151⟩.

Change to read:

TOPICAL AEROSOLS

■The following tests are applicable to topical aerosols containing drug, in suspension or solution, packaged under pressure, and released upon activation of an appropriate valve system.■1S (*USP27*)

Delivery Rate and Delivered Amount

Perform these tests only on containers fitted with continuous valves.

Delivery Rate—Select not fewer than four aerosol containers, shake, if the label includes this directive, remove the caps and covers, and actuate each valve for 2 to 3 seconds. Weigh each con-

tainer accurately, and immerse in a constant-temperature bath until the internal pressure is equilibrated at a temperature of 25° as determined by constancy of internal pressure, as directed under the *Pressure Test* below. Remove the containers from the bath, remove excess moisture by blotting with a paper towel, shake, if the label includes this directive, actuate each valve for 5.0 seconds (accurately timed by use of a stopwatch), and weigh each container again. Return the containers to the constant-temperature bath, and repeat the foregoing procedure three times for each container. Calculate the average *Delivery Rate*, in g per second, for each container.

Delivered Amount—Return the containers to the constant-temperature bath, continuing to deliver 5 second actuations to waste, until each container is exhausted. [NOTE—Ensure that sufficient time is allowed between each actuation to avoid significant canister cooling.] Calculate the total weight loss from each container. This is the *Delivered Amount.*

Pressure Test

Perform this test only on topical aerosols fitted with continuous valves.

Select not fewer than four aerosol containers, remove the caps and covers, and immerse in a constant-temperature bath until the internal pressure is constant at a temperature of 25°. Remove the containers from the bath, shake, and remove the actuator and water, if any, from the valve stem. Place each container in an upright position, and determine the pressure in each container by placing a calibrated pressure gauge on the valve stem, holding firmly, and actuating the valve so that it is fully open. The gauge is of a calibration approximating the expected pressure and is fitted with an adapter appropriate for the particular valve stem dimensions. Read the pressure directly from the gauge.

Minimum Fill

Topical aerosols meet the requirements for aerosols under *Minimum Fill* ⟨755⟩.

Leakage Test

Perform this test only on topical aerosols fitted with continuous valves.

Select 12 aerosol containers, and record the date and time to the nearest half hour. Weigh each container to the nearest mg, and record the weight, in mg, of each as W_1. Allow the containers to stand in an upright position at a temperature of 25.0 ± 2.0° for not less than 3 days, and again weigh each container, recording the weight, in mg, of each as W_2, and recording the date and time to the nearest half hour. Determine the time, T, in hours, during which the containers were under test. Calculate the leakage rate, in mg per year, of each container taken by the formula:

$$(365)(24 / T)(W_1 - W_2).$$

Where plastic-coated glass aerosol containers are tested, dry the containers in a desiccator for 12 to 18 hours, and allow them to stand in a constant-humidity environment for 24 hours prior to determining the initial weight as indicated above. Conduct the test under the same constant-humidity conditions. Empty the contents of each container tested by employing any safe technique (e.g., chill to reduce the internal pressure, remove the valve, and pour). Remove any residual contents by rinsing with suitable solvents, then rinse with a few portions of methanol. Retain as a unit the container, the valve, and all associated parts, and heat them at 100° for 5 minutes. Cool, weigh, record the weight as W_3, and determine the net fill weight ($W_1 - W_3$) for each container tested. [NOTE—If the average net fill weight has been determined previously, that value may be used in place of the value ($W_1 - W_3$) above.] The requirements are met if the average leakage rate per year for the 12 containers is not more than 3.5% of the net fill weight, and none of the containers leaks more than 5.0% of the net fill weight per year. If 1 container leaks more than 5.0% per year, and if none of the containers leaks more than 7.0% per year, determine the leakage rate of an additional 24 containers as directed herein. Not more than 2 of the 36 containers leak more than 5.0% of the net fill weight per year, and none of the 36 containers leaks more than 7.0% of the net fill weight per year. Where the net fill weight is less than 15 g and the label bears an expiration date, the requirements are met if the average leakage rate of the 12 containers is not more than 525 mg per year and none of the containers leaks more than 750 mg per year. If 1 container leaks more than 750 mg per year, but not more than 1.1 g per year, determine the leakage rate of an additional 24 containers as directed herein. Not more than 2 of the 36 containers leak more than 750 mg per year, and none of the 36 containers leaks more than 1.1 g per year. This test is in addition to the customary in-line leak testing of each container.

Total Number of Discharges per Container

Perform this test only on topical aerosols fitted with dose-metering valves, at the same time as, and on the same containers used for, the test for *Uniformity of Dosage Units* ⟨905⟩. Determine the total number of discharges or deliveries by counting the number of priming discharges plus those used in determining the spray contents, and continue to fire or discharge until the container or inhaler is empty. The requirements are met if all the containers or inhalers tested contain not less than the number of discharges stated on the label.

~~Uniformity of Dosage Units~~

■Delivered-Dose Uniformity■2S (*USP26*)

The test for ~~*Content*~~

■*Delivered-Dose*■2S (*USP26*)
Uniformity is required for topical aerosols fitted with dose-metering valves.

■For collection of the minimum dose, proceed as directed in the test for *Delivered-Dose Uniformity* under *Metered-Dose Inhalers and Dry Powder Inhalers*, as described below, except to modify the dose sampling apparatus so that it is capable of quantitatively capturing the delivered dose from the preparation being tested.■2S (*USP26*)
Unless otherwise stated in the individual monograph, apply the acceptance criteria for ~~*Metered-Dose Topical Aerosols* under *Uniformity of Dosage Units* ⟨905⟩~~

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■*Metered-Dose Inhalers and Dry Powder Inhalers* as described below.■2S (*USP26*)

Add the following:

■NASAL SPRAYS

The following test is applicable to nasal sprays, formulated as aqueous suspensions or solutions of drug, presented in multi-dose containers and fitted with dose-metering valves. In all cases, and for all tests, prepare and test the nasal spray as directed on the label and the instructions for use.

Delivered-Dose Uniformity

Unless otherwise directed in the individual monograph, the drug content of the minimum delivered doses (minimum number of sprays per nostril as described on the label, or instructions for use) collected at the beginning of unit life (after priming as described on the label, or instructions for use) and at the label claim number of metered sprays, from each of 10 separate containers, must meet the following acceptance criteria: not more than 2 of the 20 doses are outside the range of 80% to 120% of label claim, and none are outside the range of 75% to 125% of label claim, while the mean for each of the beginning and end doses falls within the range of 85% to 115% of label claim. If 3–6 doses of the 20 doses collected are outside of 80% to120% of the label claim, but none are outside of 75% to 125% of label claim, and the means for each of the beginning and end doses fall within 85% to 115% of label claim, select 20 additional containers for second-tier testing. For second-tier testing, the requirements are met if not more than 6 of the 60 doses collected are outside the range of 80% to 120% of label claim, none are outside the range of 75% to 125% of label claim, and the means for each of the beginning and end doses fall within the range of 85% to 115% of label claim.

SAMPLING FOR DELIVERED-DOSE UNIFORMITY OF METERED-DOSE NASAL SPRAYS

General Sampling Procedure—To ensure reproducible in-vitro dose collection, it is recommended that a mechanical means of actuating the pump assembly be employed to deliver doses for collection. The mechanical actuation procedure should have adequate controls for the critical mechanical actuation parameters (e.g., actuation force, actuation speed, stroke length, rest periods, etc.). The test must be performed on units that have been primed according to the patient-use instructions. The test unit should be actuated in a vertical or near vertical, valve-up, position. The two doses collected at the beginning and end of the container life should be the dose immediately following priming and the dose corresponding to the last label claim number of doses from the container.

For suspension products, the delivered dose should be delivered into a suitable container (e.g., scintillation vial) in which quantitative transfer from the container under test can be accomplished. A validated analytical method is employed to determine the amount of drug in each delivered dose, and data are reported as a percent of label claim. For solution products, the delivered dose can be determined gravimetrically from the weight of the delivered dose, and the concentration and density of the fill solution of the product under test.■1S (*USP27*)

Change to read:

METERED-DOSE INHALERS AND DRY POWDER INHALERS

The following tests are applicable to metered-dose inhalers that are formulated as suspensions or solutions of active drug in propellants and dry powder inhalers presented as single or multidose units. The following test methods are specific to the aforementioned inhalers and may require modification when testing alternative inhalation technologies (for example, breath-actuated metered-dose inhalers, or dose-metering nebulizers). However, Pharmacopeial requirements for all dose-metering inhalation dosage forms require determination of the delivered dose and *Aerodynamic Size Distribution*. In all cases, and for all tests, prepare and test the inhaler as directed on the label and the instructions for use. When

these directions are not provided by the product manufacturer, follow the precise dose discharge directions included in the tests below.

~~**Uniformity of Dosage Units**~~

■Delivered-Dose Uniformity■2S (*USP26*)

~~The test for *Dose Uniformity over the Entire Contents* is required for metered-dose inhalers and for dry-powder inhalers containing drug inhalation powders in reservoirs. Test inhalations (powders or solutions) packaged in premetereddosage units (capsules and blister packages) as directed for *Content Uniformity* under *Uniformity of Dosage Units* ⟨905⟩.~~

~~■The test for *Delivered-Dose Uniformity* is required for inhalers (e.g., metered-dose inhalers or dry powder inhalers) containing drug formulation (e.g., solution, suspension, or powder) either in reservoirs or in premetered dosage units and for drug formulations packaged in reservoirs or in premetered dosage units where these containers are labeled for use with a named inhalation device. (For inhalations packaged in premetered dosage units, see also *Uniformity of Dosage Units* ⟨905⟩.)~~

~~Unless otherwise directed in the individual monograph, the drug content of the minimum delivered dose from each of 10 separate containers is determined in accordance with the procedure described below.~~

~~Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if not less than 9 of the 10 doses are between 75% and 125% of the label claim and none is outside the range of 65% to 135% of the label claim. If the contents of not more than three doses are outside the range of 75% to 125% of the label claim, but within the range of 65% to 135% of the label claim, select 20 additional containers, and follow the prescribed procedure for analyzing one minimum dose from each. The requirements are met if not more than three results, out of the 30 values, lie outside the range of 75% to 125% of label claim and none is outside the range of 65% to 135% of the label claim.~~■2S (*USP26*)

■The test for *Delivered-Dose Uniformity* is required for inhalers (e.g., metered-dose inhalers or dry powder inhalers) containing drug formulation (e.g., solution, suspension, or powder) either in reservoirs or in premetered dosage units, and for drug formulations packaged in reservoirs or in premetered dosage units where these containers are labeled for use with a named inhalation device. (For inhalations packaged in premetered dosage units, see also *Uniformity of Dosage Units* ⟨905⟩.) Note that the target-delivered dose is the expected mean drug content for a large number of delivered doses collected from many inhalers of the chosen product. In many cases, its value may depend upon the manner in which the test for delivered dose is performed. For metered-dose inhalers, the target-delivered dose is specified by the label claim, unless otherwise specified in the individual monograph. For dry powder inhalers, where the label claim is usually the packaged or metered-dose of drug, the target-delivered dose is specified in the individual monograph and is usually less than the label claim. Its value reflects the expected mean drug content for a large number of delivered doses collected from the product, using the method specified in the monograph.

Unless otherwise directed in the individual monograph, the drug content of the minimum delivered dose from each of 10 separate containers is determined in accordance with the procedure described below.

Unless otherwise specified in the individual monograph, the requirements for dosage uniformity are met if not less than 9 of the 10 doses are between 75% and 125% of the specified target-delivered dose and none is outside the range of 65% to 135% of the specified target-delivered dose. If the contents of not more than 3 doses are outside the range of 75% to 125% of the specified target-delivered dose, but within the range of 65% to 135% of the specified target-delivered dose, select 20 additional containers, and follow the

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prescribed procedure for analyzing 1 minimum dose from each. The requirements are met if not more than 3 results, out of the 30 values, lie outside the range of 75% to 125% of the specified target-delivered dose, and none is outside the range of 65% to 135% of the specified target-delivered dose.■1S (*USP27*)

~~DOSAGE UNIT SAMPLING FOR METERED-DOSE INHALERS~~

■SAMPLING THE DELIVERED DOSE FROM METERED-DOSE INHALERS■2S (*USP26*)

To determine the content of active ingredient in the discharged spray from a metered-dose inhaler, use the sampling apparatus described below, using a flow rate of 28.3 L of air per minute (±5%), unless otherwise stated in the individual monograph.

Apparatus A—The apparatus (see *Figure 1*) consists of a filter support base with an open-mesh filter support, such as a stainless steel screen, a collection tube that is clamped or screwed to the filter support base, and a mouthpiece adapter to ensure an airtight seal between the collection tube and the mouthpiece. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the sample collection tube. The vacuum connector is connected to a system comprising a vacuum source, flow regulator, and flowmeter. The source should be capable of pulling air through the complete assembly, including the filter and the inhaler to be tested, at the desired flow rate. When testing metered-dose inhalers, air should be drawn continuously through the system to avoid loss of drug into the atmosphere. The filter support base is designed to accommodate 25-mm diameter filter disks. At the airflow being used, the sample collection tube and the filter disk must be capable of quantitatively collecting the delivered dose. The filter disk and other materials used in the construction of the apparatus must be compatible with the drug and the solvents that are used to extract the drug from the filter. One end of the collection tube is designed to hold the filter disk tightly against the filter support base. When assembled, the joints between the components of the apparatus are airtight so that when a vacuum is applied to the base of the filter, all of the air drawn through the collection device passes through the inhaler.

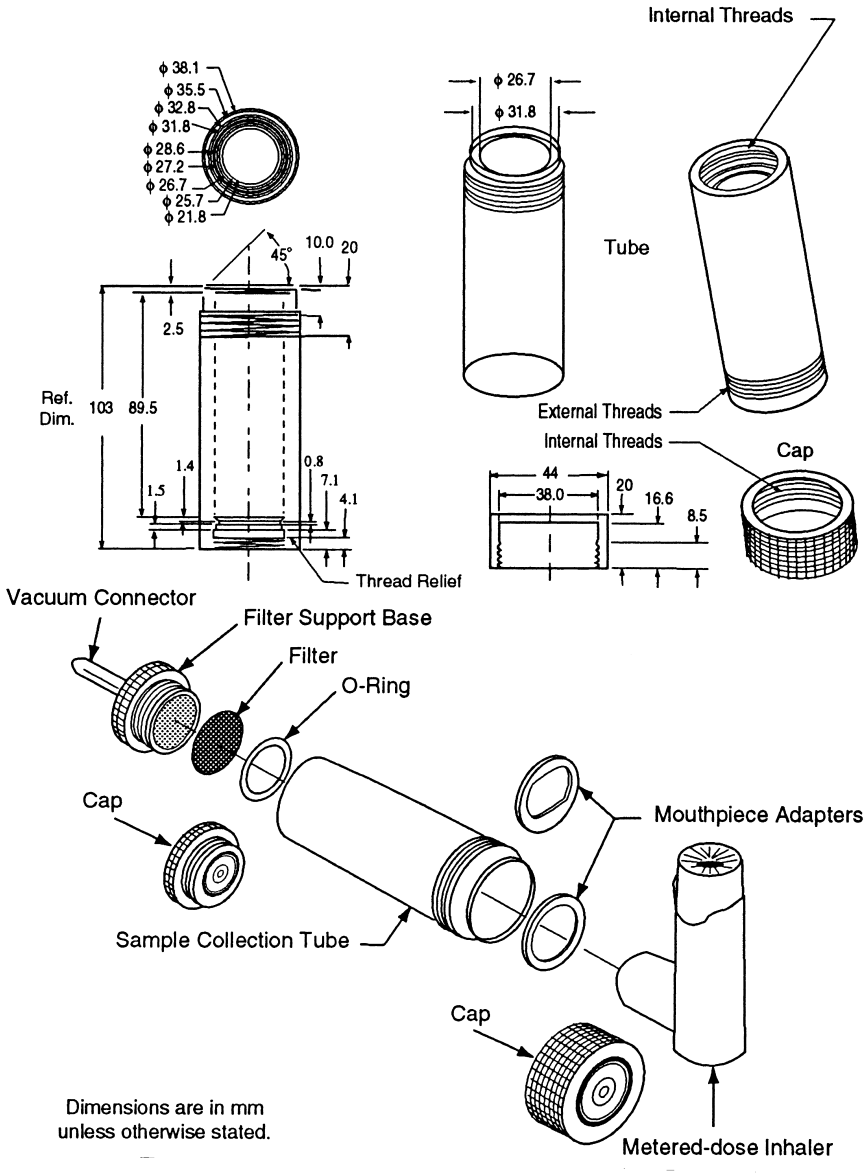

Fig. 1. Sampling apparatus for pressurized metered-dose inhalers

Procedure—

■Prepare the inhaler for use according to the label instructions.■2S (*USP26*)
Unless otherwise specified in the individual monograph, with the vacuum pump running, ensuring an airflow rate through the inhaler of 28.3 L of air per minute (±5%), discharge the minimum recommended dose into the apparatus through the mouthpiece adapter by depressing the valve for a duration sufficient to ensure that the dose has been completely discharged. Detach the inhaler from *Apparatus A*, and disconnect the vacuum. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent.

~~DOSAGE UNIT SAMPLING FOR DRY POWDER INHALERS~~

■SAMPLING THE DELIVERED DOSE FROM DRY POWDER INHALERS■2S (*USP26*)

To determine the content of active ingredient emitted from the mouthpiece of a dry powder inhaler, use *Apparatus B* (see *Figure 2*). This apparatus is capable of sampling the emitted doses at a variety of airflow rates.

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Change to read:

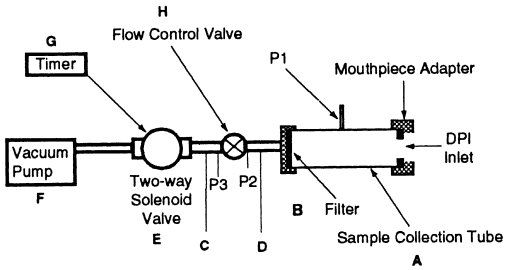

Fig. 2. Apparatus B: ~~Dosage unit sampling~~

■Sampling■2S (*USP26*)
apparatus for dry powder inhalers. (See *Table 1* for component specifications.)

Table 1. Component Specifications for Apparatus B (see *Figure 2*)

Code	Item	Description	Dimensions
A	Sample collection tube[a]	See *Fig. 2*	34.85-mm ID × 12-cm length
B	Filter[b]	See *Fig. 2*	47-mm glass fiber filter
C	Connector	(e.g., short metal coupling with low diameter branch to P3)	≥8-mm ID
D	Vacuum tubing	(e.g., silicon tubing with an outside diameter of 14 mm and an internal diameter of 8 mm)	8 ± 0.5-mm ID × 50 ± 10-cm length
E	Two-way solenoid valve[c]	See *Fig. 2*	Minimum airflow orifice having an internal diameter of ≥8 mm and a maximum response time of 100 milliseconds
F	Vacuum pump[d]	See *Fig. 2*	Pump must be capable of drawing the required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to the solenoid valve using short and wide (≥10-mm ID) vacuum tubing and connectors to minimize pump capacity requirements.
G	Timer[e]	See *Fig. 2*	The timer switches current directly to the solenoid valve for the required duration.
P1	pressure tap	See *Fig. 2*	2.2-mm ID, 3.1-mm OD flush with the internal surface of the sample collection tube, centered and burr free, 59.0 mm from its inlet
P1, P2, P3	pressure measurements[f]		
H	Flow-control valve[g]	See *Fig. 2*	Adjustable regulating valve with maximum $C_v \geq 1$[h]

[a] An example being a Millipore product number XX40 047 00 (Millipore Corporation, 80, Ashby Road, Bedford, MA 01732), modified so that the exit tube has an ID ≥ 8-mm, fitted with Gelman product number 61631.
[b] A/E (Gelman Sciences Inc., 600 South Wagner Road, Ann Arbor, MI 48106) or equivalent.
[c] ASCO product number 8030G13, Automatic Switch Company, 60 HanoverRoad, Florham Park, NJ 07932.
[d] Gast product type 1023, 1423, or 2565 (Gast Manufacturing Inc., PO Box 97, Benton Harbor, MI 49022) or equivalent.
[e] Eaton Product number 45610-400 (Eaton Corporation, Automotive Products Division, 901, South 12th Street, Watertown, WI 53094) or equivalent.
[f] An example being a PDM 210 pressure meter (Air-Neotronics Ltd., Neotronics Technology plc, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU, UK), or equivalent.
[g] Parker Hannifin type 8FV12LNSS (Parker Hannifin plc., Riverside Road, Barnstable, Devon EX31 1NP, UK) or equivalent.
[h] Flow Coefficient, as defined by ISA S75.02 "Control valve capacity test procedure" in *Standards and Recommended Practices for Instrumentation and Control*, 10th ed., Vol. 2, 1989. Published by Instrument Society of America, 67 Alexander Drive, P.O. Box 1227, Research Triangle Park, NC 27709, U.S.A.

Apparatus B—The apparatus is similar to that described in *Figure 1* for testing metered-dose inhalers. In this case, however, the filter and collection tube have a larger internal diameter to accommodate 47-mm diameter filter disks. This feature enables dosage collection at higher airflow rates—up to 100 L of air per minute—when necessary. A mouthpiece adapter ensures an airtight seal between the collection tube and the mouthpiece of the dry powder inhaler being tested. The mouthpiece adapter must ensure that the tip of the inhaler mouthpiece is flush with the open end of the sample collection tube. Tubing connectors, if they are used, should have an internal diameter greater than or equal to 8 mm to preclude their own internal diameters from creating significant airflow resistance. A vacuum pump with excess capacity must be selected in order to draw air, at the designated volumetric flow rate, through both the sampling apparatus and the inhaler simultaneously. A timer-controlled, low resistance, solenoid-operated, two-way valve is interposed between the vacuum pump and the flow-control valve to control the duration of flow. This type of valve enables 4.0 L of air ($\pm 5\%$) to be withdrawn from the mouthpiece of the inhaler at the designated flow rate. Flow control is achieved by ensuring that critical (sonic) flow occurs in the flow-control valve (absolute pressure ratio P3/P2 ≤ 0.5 under conditions of steady-state flow).

Procedure—Operate the apparatus at an airflow rate~~, Q,~~

■■1S (*USP27*)
which produces a pressure drop of 4 kPa (40.8 cm H_2O) over the inhaler to be tested, and a duration~~, T,~~

■■1S (*USP27*)
consistent with the withdrawal of 4 L of air from the mouthpiece of the inhaler. ~~[NOTE—If Q and T are defined otherwise in the monograph, use values of Q and T that are within 5% of those values. Determine the value of Q.]~~

■[NOTE—If the flow rate and duration are defined otherwise in the monograph, adjust the system to within 5% of those values.] Determine the test flow rate■1S (*USP27*)
using *Apparatus B* as follows. Insert an inhaler into the mouthpiece adapter to ensure an airtight seal. In cases where the drug packaging modifies the inhaler's resistance to airflow, use a loaded, drug-free inhaler (with previously emptied packaging). In other cases, use an unloaded (drug free) inhaler. Connect one port of a differential pressure transducer to the pressure tap, P1, and leave the other open to the atmosphere. Switch on the pump, and open the two-way solenoid valve. Adjust the flow-control valve until the pressure drop across the inhaler is 4.0 kPa (40.8 cm H_2O). Ensure that critical (sonic) flow occurs in the flow-control valve by determining the individual values for absolute pressure, P2 and P3, so that their ratio P3/P2 is less than or equal to 0.5. If this criterion cannot be achieved, it is likely that the vacuum pump is worn or of insufficient capacity. Critical (sonic) flow conditions in the flow-control valve are required in order to ensure that the volumetric airflow ~~is unaffected by pump fluctuations and minor changes in airflow resistance at the inhaler inlet.~~

■drawn from the mouthpiece is unaffected by pump fluctuations and changes in airflow resistance of the inhaler.■1S (*USP27*)
Remove the inhaler from the mouthpiece adapter and, without disturbing the flow-control valve, measure the airflow rate, ~~Q, by connecting a flowmeter~~

■drawn from the mouthpiece, Q_{out}, by connecting a flowmeter to the mouthpiece adaptor in an airtight fashion. Use a flowmeter■1S (*USP27*)
calibrated for the volumetric flow leaving the meter ~~to the mouthpiece adapter in an airtight fashion~~

■to directly determine Q_{out} or, if such a meter is unobtainable, calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For example, for a meter calibrated for the entering volumetric flow (Q_{in}), use the formula:

$$Q_{out} = Q_{in} P_0 / (P_0 - \Delta P),$$

where P_0 is the atmospheric pressure and ΔP is the pressure drop over the meter.■1S (*USP27*)
If the flow rate is greater than 100 L of air per minute, adjust the flow-control valve until ~~Q~~

■Q_{out}■1S (*USP27*)
equals 100 L per minute; otherwise, record the value of ~~Q~~

■Q_{out},■1S (*USP27*)
and leave the flow-control valve undisturbed. Define the test flow duration, ~~$T = 240/Q$~~

■$T = 240/Q_{out}$,■1S (*USP27*)
in seconds, so that a volume of 4.0 L of air ($\pm 5\%$) is withdrawn from the inhaler ~~during the withdrawal of the test dose~~

■at the test flow rate Q_{out},■1S (*USP27*)
and adjust the timer controlling the operation of the two-way solenoid valve accordingly. Prime or load the inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the solenoid valve closed, insert the inhaler mouthpiece horizontally into the mouthpiece adapter. Discharge the powder into the sampling apparatus by activating the timer controlling the solenoid valve and withdrawing 4.0 L of air from the inhaler at the previously defined airflow rate. If the labeled instructions so direct, repeat the operation so as to simulate the use of the inhaler by the patient (e.g., inhale two or three times, if necessary, to empty the capsule). Repeat the whole operation n –1 times beginning with the text, ''Prime or load the inhaler with powder,'' where n is the number of times defined in the labeling as the minimum recommended dose. Detach the dry powder inhaler from the sampling apparatus, and disconnect the vacuum tubing, D. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent. Where specified in individual monographs, perform this test under conditions of controlled temperature and humidity.

■Delivered-■2S (*USP26*)

Dose Uniformity over the Entire Contents

~~This test is required for metered-dose inhalers and dry powder inhalers containing drug inhalation powders either in reservoirs or as premetered dosage units. Note that inhalations (powders or so-~~

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~~lutions) packaged in premetered dosage units (capsules and blister packages) must also meet the requirements under *Uniformity of Dosage Units* ⟨905⟩.~~The test for

■*Delivered-*■2S (*USP26*)
Dose Uniformity over the Entire Contents ~~also ensures that multidose products supply the total number of discharges stated on the label.~~

■is required for inhalers (e.g., metered-dose inhalers or dry powder inhalers) containing multiple doses of drug formulation (e.g., solution, suspension, or dry powder) either in reservoirs or in premetered dosage units (e.g., blisters), and for drug formulations packaged in reservoirs or in multiple-dose assemblies of premetered dosage units that have a predetermined dose sequence, where these multiple-dose assemblies are labeled for use with a named inhalation device. The test for *Delivered-Dose Uniformity over the Entire Contents* also ensures that multidose products supply the total number of discharges stated on the label.■2S (*USP26*)
Unless otherwise directed in the individual monograph, the drug content of at least 9 of the 10 doses collected from one inhaler, in accordance with the procedure below, are between 75% and 125% of ~~label claim~~

■the target-delivered dose,■1S (*USP27*)
and none is outside the range of 65% to 135% of ~~label claim~~

■the target-delivered dose.■1S (*USP27*)
If the contents of not more than 3 doses are outside the range of 75% to 125%, but within the range of 65% to 135% of ~~label claim~~

■the target-delivered dose,■1S (*USP27*)
select 2 additional inhalers, and follow the prescribed procedure for analyzing 10 doses from each. The requirements are met if not more than 3 results, out of the 30 values, lie outside the range of 75% to 125% of ~~label claim~~

■the target-delivered dose,■1S (*USP27*)
and none is outside the range of 65% to 135% of ~~label claim.~~

■the target-delivered dose.■1S (*USP27*)

METERED-DOSE INHALERS

Apparatus—Use *Apparatus A* as directed in ~~*Dosage Unit Sampling for Metered-Dose Inhalers* under *Uniformity of Dosage Units* ⟨905⟩~~

■*Sampling the Delivered-Dose from Metered-Dose Inhalers* under *Delivered-Dose Uniformity*■2S (*USP26*)
at a flow rate of 28.3 L of air per minute (±5%).

Procedure—A single dose is defined as the number of sprays specified in the product labeling as the minimum recommended dose. ~~To determine the minimum dosing interval in hours, divide 24 hours by the maximum number of doses permitted per day, as stated in the labeling.~~

■■2S (*USP26*)
Select a single metered-dose inhaler, and follow the labeled instructions for priming, shaking, cleaning, and firing the inhaler throughout. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds, and fire one minimum recommended dose to waste. ~~Allow the inhaler to stand in either the valve up or valve down position, unless directed otherwise in the labeling, for the minimum dosing interval, or longer, and collect the next dose.~~

■Wait for 5 seconds, and collect the next dose.■2S (*USP26*)
Detach the inhaler from *Apparatus A*, and disconnect the vacuum. Assay the contents of the apparatus for drug after rinsing the filter and the interior of the apparatus with a suitable solvent. Collect two more doses, allowing ~~the inhaler to stand for the minimum dosing interval, or longer, before collecting each dose.~~

■at least 5 seconds between doses.■2S (*USP26*)
Discharge the device to waste, waiting for not less than 5 seconds between actuations

■(unless otherwise specified in the individual monograph),■2S (*USP26*)
until $(n/2) + 1$ minimum recommended doses remain, in which n is the number of minimum recommended doses on the label. Collect four more doses, allowing ~~the inhaler to stand for the minimum dosing interval, or longer, before collecting each dose.~~

■at least 5 seconds between doses, unless otherwise specified in the individual monograph.■2S (*USP26*)
Discharge the device to waste, as before, until three doses remain. Collect the final three doses, allowing ~~the inhaler to stand for the minimum dosing interval, or longer, before collecting each dose. Note that in order to test within a reasonable time frame, there is no need to wait for the minimum dosing interval before expelling doses to waste. However, the rate of discharges to waste should not cause excessive canister cooling.~~

■at least 5 seconds between doses. Note that the rate of discharges to waste should not be such to cause excessive canister cooling.■2S (*USP26*)

DRY POWDER INHALERS

Apparatus—Use *Apparatus B* as directed in ~~Dosage Unit Sampling for Dry Powder Inhalers under *Uniformity of Dosage Units* ⟨905⟩~~

■*Sampling the Delivered Dose from Dry Powder Inhalers* under *Delivered-Dose Uniformity*■2S (*USP26*)
at the appropriate airflow rate for testing.

Procedure—~~For dry powder inhalers that contain multiple-dose reservoirs of dry powder, collect single doses, and proceed as directed for *Procedure* in the *Dosage Unit Sampling for Dry Powder Inhalers* under *Uniformity of Dosage Units* ⟨905⟩.~~

■Proceed as directed for *Procedure* in *Sampling the Delivered Dose from Dry Powder Inhalers* under *Delivered-Dose Uniformity.*■2S (*USP26*)
A single dose is defined as the number of actuations stated in the product labeling as the minimum recommended dose. Select a single inhaler and follow the labeled instructions for loading with powder, discharging and cleaning throughout. Collect a total of 10 doses—three doses at the beginning, four in the middle [(n/2) – 1 to (n/2) + 2, where n is the number of minimum recommended doses on the label], and three at the end—of the labeled contents following the labeled instructions.[+] ~~Allow the inhaler to stand in the upright position for the minimum dosing interval, or longer, as defined for *Procedure* above for metered-dose inhalers, before collecting each dose. In order to enable testing within a reasonable time frame, there is no need to wait for the minimum dosing interval before expelling a dose to waste.~~
■■2S (*USP26*)
Prior to collecting each of the doses to be analyzed, clean the inhaler as directed in the labeling.

Change to read:

Particle Size

The particle or droplet size distribution in the spray discharged from metered-dose inhalers, and the particle size distribution in the cloud discharged from dry powder inhalers, are important characteristics used in judging inhaler performance. While particle size measurement by microscopy can be used to evaluate the number of large particles, agglomerates, and foreign particulates in the emissions of metered-dose inhalers (e.g., *Epinephrine Bitartrate Inhalation Aerosol*), whenever possible this test should be replaced with a method to determine the aerodynamic size distribution of the drug aerosol leaving the inhaler. The aerodynamic size distribution defines the manner in which an aerosol deposits during inhalation. When there is a log-normal distribution, the aerodynamic size distribution may be characterized by the mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). The aerodynamic size distribution of the drug leaving metered-dose and dry powder inhalers is determined using *Apparatus 1*, *2*, *3*, ~~or *4*~~

■*4*, *5*, or *6*■1S (*USP27*)
as specified in this chapter. A fine particle dose or fine particle fraction can also be determined as that portion of the inhaler output having an aerodynamic diameter less than the size defined in the individual monograph. This may be expected to correlate with the drug dose or that fraction of the drug dose that penetrates the lung during inhalation. Individual monographs may also define the emitted fractions of the delivered dose in more than one aerodynamic size range.

AERODYNAMIC SIZE DISTRIBUTION

Cascade impaction devices classify aerosol particles and droplets on the basis of those particles' aerodynamic diameters. The principle of their operation, whereby they separate aerosol particles and droplets from a moving airstream on the basis of particle or droplet inertia, is shown in *Figure 3.* Because the dimensions of the induction port used to connect inhalers to the cascade impactors and impingers ~~(shown in *Apparatus 1*, *2*, *3*, *4* and~~

■(shown in *Apparatus 1*, *2*, *3*, *4*, *5*, and *6*)■1S (*USP27*)
also define the mass of drug that enters the aerodynamic sizing device, these are carefully defined and, where possible, are held constant between each apparatus (see *Figures 4*, *6*, *7*, ~~*8*, and~~

■*8*, and *9*).■1S (*USP27*)
Because the size distributions produced by different impactors are often a function of impactor design and the airflow rate through them, there is a need to standardize the instruments that are used to test inhalers ~~(i.e., *Apparatus 1* for metered-dose inhalers)~~

■(i.e., *Apparatus 1* or *6* for metered-dose inhalers)■1S (*USP27*)
or to provide guidelines on system suitability where different apparatuses may be used ~~(i.e., *Apparatus 2*, *3*, or *4* for dry powder inhalers).~~

■(i.e., *Apparatus 2*, *3*, *4*, or *5* for dry powder inhalers).■1S (*USP27*)

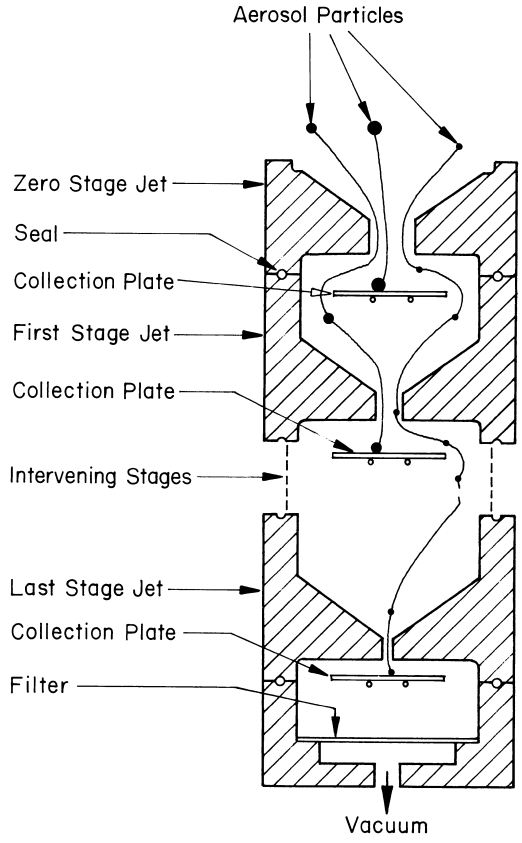

Fig. 3. Schematic representation of the principle of operation of cascade impactors. (A single jet per impactor stage is shown. Impactors with multiple jets in each stage function in the same manner.)

[+] ~~Dry powder inhalers designed to accept separately packaged single doses of inhalation powder only, in which there is no predetermined dosing sequence, are tested by collecting 10 sequential minimum recommended doses.~~

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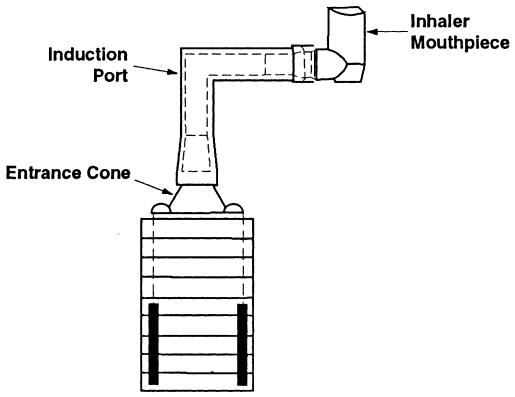

Fig. 4. Apparatus 1: Assembly of induction port and entrance cone mounted on cascade impactor.

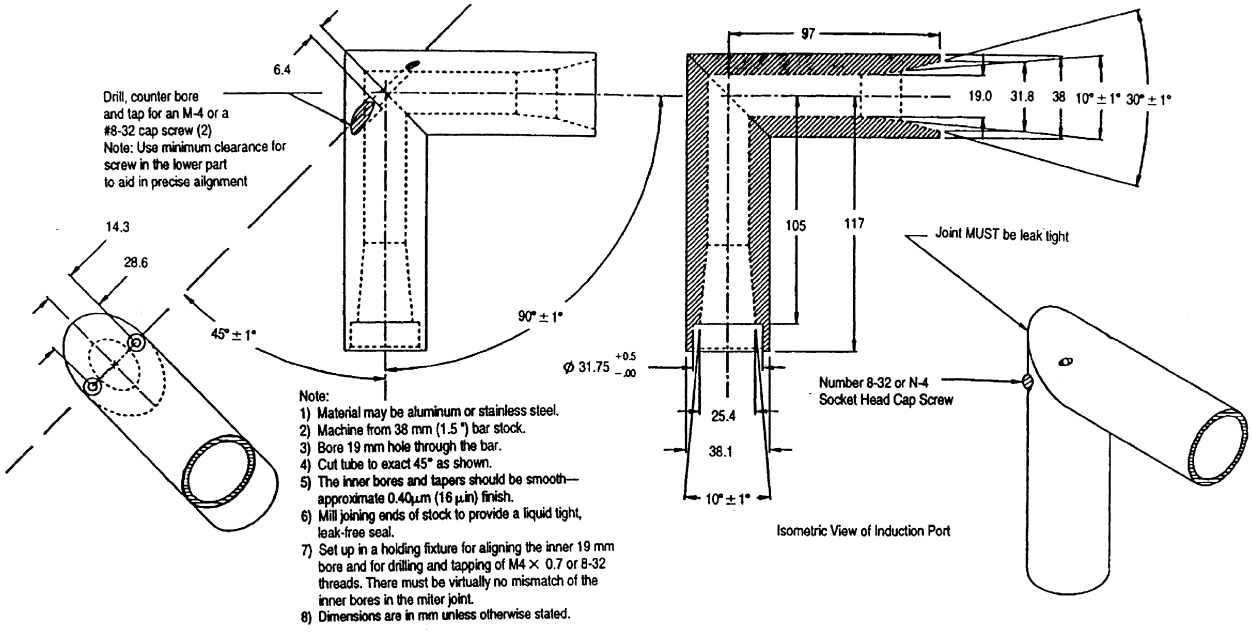

Fig. 4a. Apparatus 1: Expanded view of induction port for use with metered-dose and dry powder inhalers.

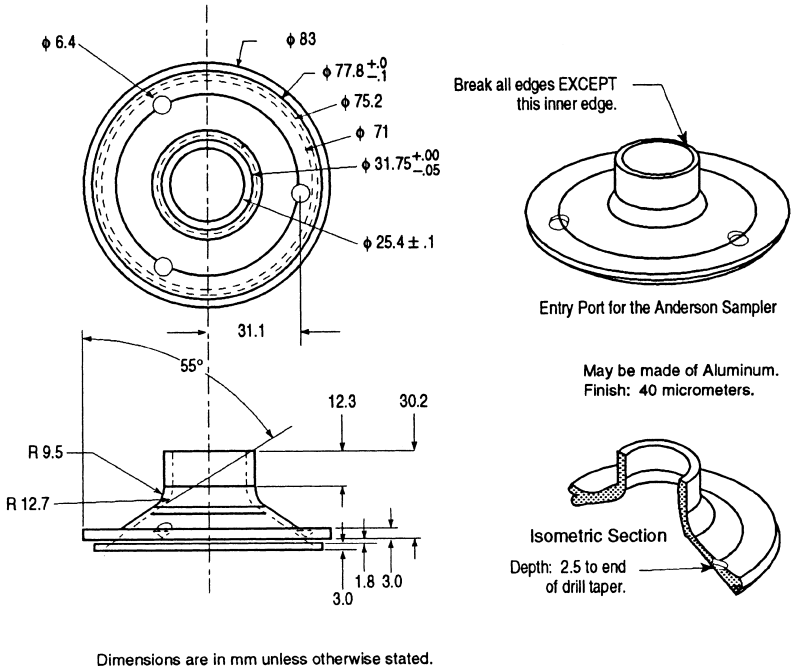

Fig. 4b. Apparatus 1: Expanded view of the entrance cone for mounting induction port on the Andersen cascade impactor without pre-separator.[2]

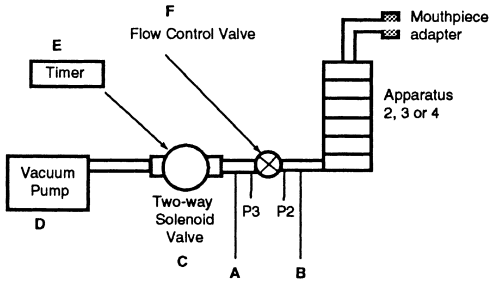

Fig. 5. Apparatus 2, 3, and 4: General control equipment. (See *Table 2* for component specifications.)

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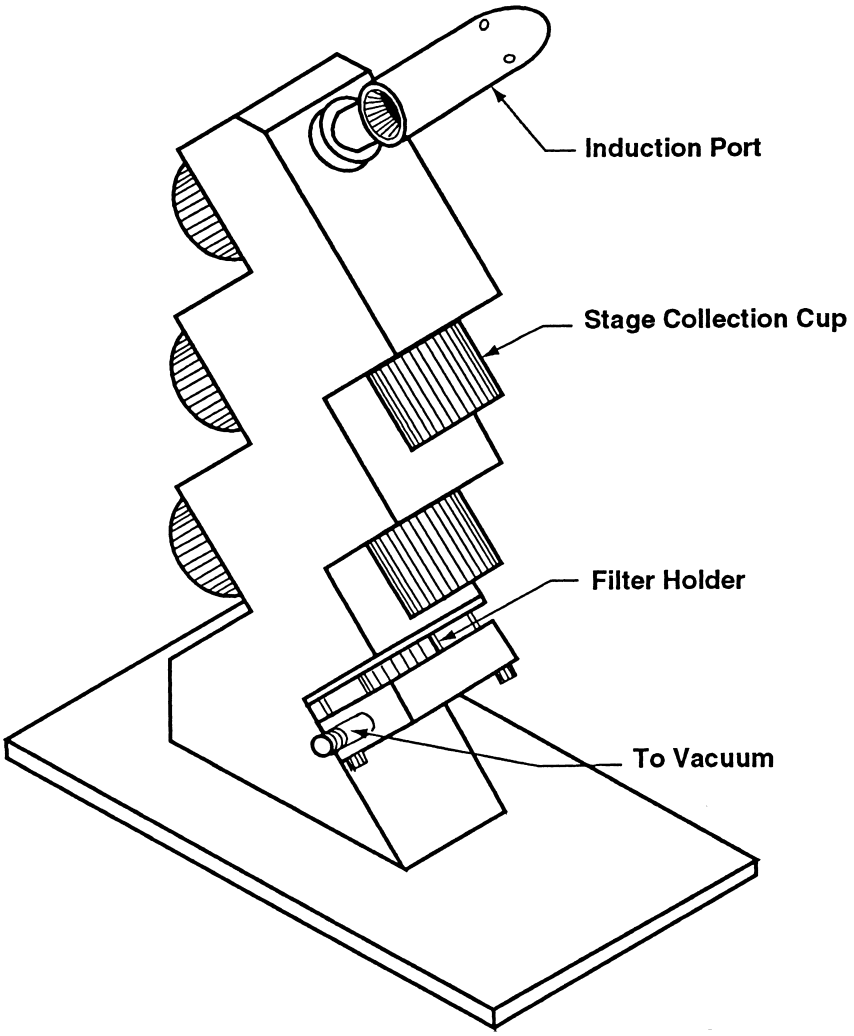

Fig. 6. Apparatus 2: Assembly of induction port, stage collector, and filter holder. (Marple-Miller impactor, Model 160 with USP induction port.)

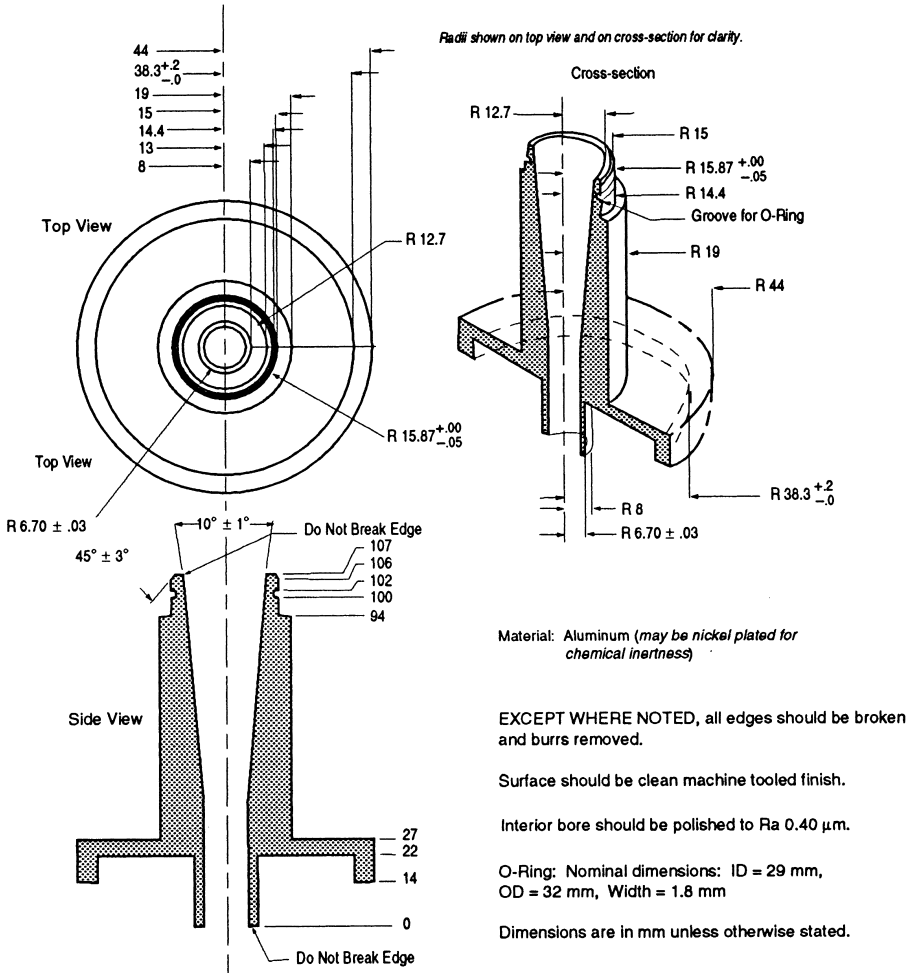

Fig. 7. Apparatus 3: Expanded views of top for the Andersen preseparator adapted to the USP induction port.

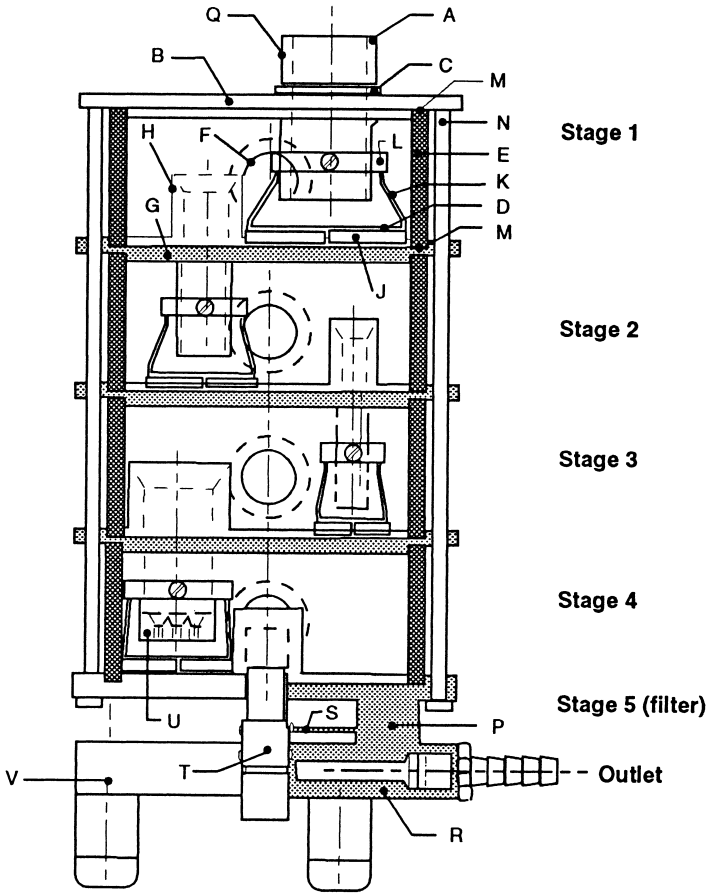

Fig. 8. Apparatus 4: Schematic of multistage liquid impinger. (See *Table 3* for component specifications.)

~~**System Suitability**~~

■■2S (*USP26*).

Because of the varied nature of the formulations and devices being tested, the cascade impaction system and technique selected for testing an inhaler should fulfill a number of criteria.

Stage Mensuration—Manufacturers of cascade impaction devices provide a definitive calibration for the separation characteristics of each impaction stage in terms of the relationship between the stage collection efficiency and the aerodynamic diameter of particles and droplets passing through it as an aerosol. Calibration is a property of the jet dimensions, the spatial arrangement of the jet and its collection surface, and the airflow rate passing through it. Because jets can corrode and wear over time, the critical dimensions of each stage, which define that impaction stage's calibration, must be measured on a regular basis. This process, known as stage mensuration, replaces the need for repetitive calibration (using standard aerosols) and ensures that only devices that conform to specifications are used for testing inhaler output. The process involves the measurement and adjustment of the critical dimensions of the instrument.

Interstage Drug Loss (wall losses)—Where method variations are possible and there is no apparatus specified in the monograph, the selected technique should ensure that not more than 5% of the inhaler's total delivered drug mass (into the impactor) is subject to loss between the impaction device's sample collection surfaces. In the event that interstage drug losses are known to be greater than 5%, either the procedure should be performed in such a way that wall losses are included along with the associated collection plate, or an alternative apparatus should be used. As an example, the following procedures described for *Apparatus 1* and *3* have been written to include wall losses along with the associated collection plate. Provided, however, that such losses are known to be less than or equal to 5% of the total delivered drug mass into the impactor and that there are no instructions to the contrary in an individual monograph, the technique may be simplified by only assaying drug on the collection plates.

Re-Entrainment—Where method variations are possible, the selected technique should seek to minimize particle re-entrainment (from an upper to a lower impaction stage) on stages that contribute to size fractions defined in the individual monograph, especially where this may affect the amounts of drug collected. Minimizing the number of sampled doses, the use of coated particle collection surfaces, and proving that multiple-dose techniques produce statistically similar results to those from smaller numbers of doses, are all methods that can be used for this purpose. In the event that re-entrainment cannot be avoided, the number of doses collected, the time interval between doses, and the total duration of airflow through the cascade impaction device should be standardized. Under these circumstances, the presentation of impaction data should not presume the validity of the impactor's calibration (i.e., aerodynamic diameter ranges should not be assigned to drug masses collected on specific stages).

By using appropriate assay methods and a suitable mensurated impaction device, aerodynamic particle size distributions can be determined for drugs leaving the mouthpieces of metered-dose or dry powder inhalers. If temperature or humidity limits for use of the inhaler are stated on the label, it may be necessary to control

the temperature and humidity of the air surrounding and passing through the device to conform to those limits. Ambient conditions are presumed, unless otherwise specified in individual monographs. ~~In addition to the size distribution, good analytical practice dictates that a complete mass balance must be performed in order to confirm that all of the drug discharged from the inhaler was captured and measured in the induction port-cascade impactor apparatus. This is not a test of the inhaler but serves to ensure that the test results are valid.~~

■*Mass Balance*—In addition to the size distribution, good analytical practice dictates that a mass-balance be performed in order to confirm that the amount of the drug discharged from the inhaler, which is captured and measured in the induction port-cascade impactor apparatus, is within an acceptable range around the ~~label claim~~ ■expected value.■1S (*USP27*) The total mass of drug collected in all of the components (material balance) divided by the total number of minimum recommended doses discharged is not less than 75% and not more than 125% of the average minimum recommended dose determined during testing for *Delivered-Dose Uniformity*. This is not a test of the inhaler but serves to ensure that the test results are valid.■2S (*USP26*)

Use one of the multistage impaction devices shown below, or an equivalent, to determine aerodynamic particle size distributions of drugs leaving the mouthpieces of metered-dose or dry powder inhalers. ~~*Apparatus 1* (*Figure 4*) is~~

■*Apparatus 1* and *6* [*Figures 4* and *9* (without preseparator), respectively] are■1S (*USP27*) intended for use with metered-dose inhalers at a single airflow rate. ~~*Apparatus 2*, *3*, and *4* (Figures *6*, *7*, and *8*, respectively)~~

■*Apparatus 2*, *3*, *4*, and *5* (*Figures 6*, *7*, *8*, and *9*, respectively)■1S (*USP27*) are intended for use with dry powder inhalers at the appropriate airflow rate, ~~*Q* determined earlier, provided that the value of *Q*~~

■Q_{out}, determined earlier, provided that the value of Q_{out}■1S (*USP27*) falls in the range 30–100 L per minute.

~~NOTE—If *Q* is greater than 100 L per minute, testing should be performed at 100 L per minute; if *Q* < 30 L per minute, testing is performed at 30 L per minute.~~

■NOTE—If Q_{out} is greater than 100 L per minute, testing should be performed with Q_{out} set at 100 L per minute; if Q_{out} is less than 30 L per minute, testing is performed with Q_{out} at 30 L per minute.■1S (*USP27*)

Apparatus 1 for Metered-Dose Inhalers—Use this apparatus, or an equivalent, at a flow rate of 28.3 L per minute (±5%), as specified by the manufacturer of the cascade impactor.

Design—The design and assembly of this apparatus and the induction port to connect the device to an inhaler are shown in *Figures 4*, *4a*, and *4b*[2].

Procedure—Set up the multistage cascade impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device.

■To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary.■1S (*USP27*) Attach the induction port and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port as shown in *Figure 4*. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks. Turn on the vacuum pump to draw air through the cascade impactor, and calibrate the airflow through the system with an appropriate flowmeter attached to the open end of the induction port. Adjust the flow-control valve on the vacuum pump to achieve steady flow through the system at the required rate, and ensure that the airflow through the system is within ±5% of the flow rate specified by the manufacturer. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds and discharge one delivery to waste. With the vacuum pump running, insert the mouthpiece into the mouthpiece adapter and immediately fire the minimum recommended dose into the cascade impactor. Keep the valve depressed for a duration sufficient to ensure that the dose has been completely discharged. If additional sprays are required for the sample, wait for 5 seconds before removing the inhaler from the mouthpiece adapter, shake the inhaler, reinsert it into the mouthpiece adapter, and immediately fire the next minimum recommended dose. Repeat until the required number of doses have been discharged. The number of minimum recommended doses discharged must be sufficient to ensure an accurate and precise determination of *Aerodynamic Size Distribution*. [NOTE—The number of minimum recommended doses is typically not greater than 10.] After the last dose has been discharged, remove the inhaler from the mouthpiece adapter. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume. Disassemble the cascade impactor, place each stage and its associated collection plate or filter in a separate container, and rinse the drug from each of them. [NOTE—If it has been determined that wall losses in the impactor are less than or equal to 5%, then the collection plates only may be used.] ~~see *System Suitability* above.~~

■■2S (*USP26*)
Dilute each quantitatively to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the components. ~~The total mass of drug collected in all of the components (material bal-~~

[2] A suitable cascade impactor is available as Model Mk II from Graseby Inc., 500 Technology Court, Smyrna, GA, 30082. The impactor is used without the preseparator. The inhaler is connected to the impactor via the induction port, atop the entrance cone shown in *Figure 4*. If an equivalent impactor is employed, the induction port in *Figure 4a* should be used, although the entrance cone (*Figure 4b*) should be replaced with one to fit the impactor in question. Note that the internal surfaces of the induction port (*Figure 4a*) are designed to fit flush with their counterparts in the entrance cone (*Figure 4b*). This design avoids aerosol capture at the junction of the two pipes.

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~~ance) divided by the total number of minimum recommended doses discharged is not less than 75% and not more than 125% of the average minimum recommended dose determined during testing for *Uniformity of Dosage Units*. If the total mass is outside of the acceptable range, the test must be repeated.~~

■■2S (*USP26*)
To analyze the data, proceed as directed under *Data Analysis*.

Apparatus 2 for Dry Powder Inhalers—

Design—The design and assembly of *Apparatus 2*, and the induction port to connect the device to an inhaler, are shown in *Figure 6*.[3] [NOTE—The induction port is shown in detail in *Figure 4a*.] The impactor has five impaction stages and an after filter. At a volumetric airflow rate of 60 L per minute (the nominal flow rate, Q_n), the cutoff aerodynamic diameters $D_{50,Qn}$ of Stages 1 to 5 are 10, 5, 2.5, 1.25, and 0.625 µm, respectively. The after filter effectively retains aerosolized drug in the particle size range up to 0.625 µm. Set up the multistage cascade impactor with the control system as specified in *Figure 5*. ~~If necessary, coat the particle collection surface of each of the stages to ensure that particles that impact on a given stage are not re-entrained in the flowing airstream. Assemble the impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. Attach the induction port and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks.~~

■To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary.■1S (*USP27*)
Assemble the impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. Attach the induction port and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks.

Turn on the vacuum pump, open the solenoid valve, and calibrate the airflow through the system as follows. Connect a flowmeter ~~calibrated for the volumetric flow rate leaving the meter,to the induction port.~~

■to the induction port. Use a flowmeter calibrated for the volumetric flow leaving the meter to directly determine Q_{out}, or, if such a meter is unobtainable, calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For example, for a meter calibrated for the entering volumetric flow (Q_{in}), use the formula:

$$Q_{out} = Q_{in}P_0 / (P_0 - \Delta P),$$

where P_0 is the atmospheric pressure and ΔP is the pressure drop over the meter. ■1S (*USP27*)
Adjust the flow-control valve to achieve a steady flow through the system at the required rate, ~~Q, so that Q~~

■Q_{out}, so that Q_{out}■1S (*USP27*)
is within ±5% of the value determined during testing for ~~*Uniformity of Dosage Units*~~.

■*Delivered-Dose Uniformity.*■2S (*USP26*)
Ensure that critical flow occurs in the flow-control valve, at the ~~value of Q to be used during testing,~~

■airflow rate to be used during testing, by■1S (*USP27*)
using the following procedure. With the inhaler in place, and the intended flow running, measure the absolute pressure on both sides of the flow-control valve (P2 and P3 in *Figure 5*). A ratio of P3/P2 ≤ 0.5 indicates critical flow. Switch to a more powerful pump, and remeasure the test flow rate if P3/P2 > 0.5. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens this valve for a duration of T seconds

■as determined during testing for *Delivered-Dose Uniformity.*■1S (*USP27*)
Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by opening the two-way solenoid valve for a duration of T seconds. After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume. Disassemble the cascade impactor, and place the after filter in a separate container. Rinse the drug from each of the stages and the filter, and dilute each quantitatively to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the components. ~~The total mass of drug collected in all of the components (material balance) divided by the total number of minimum recommended doses discharged is not less than 75% and not more than 125% of the average minimum recommended dose determined during testing for *Uniformity of Dosage Units*. If the total mass is outside of the acceptable range, the test must be repeated.~~

■■2S (*USP26*)
Determine the cutoff diameters of each of the individual stages of the impactor, at the value of ~~Q~~

■$Q = Q_{out}$■1S (*USP27*)
employed in the test by the formula:

$$D_{50,Q} = D_{50,Qn}(Q_n / Q)^{1/2}, \quad \text{(Eq. 1)}$$

where $D_{50,Q}$ is the cutoff diameter at the flow rate, Q, employed in the test, and the subscript, n, refers to the nominal values determined when Q_n equals 60 L per minute. Thus, when Q equals 40 L per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,40LPM} = 5\ \mu m \times [60/40]^{1/2} = 6.1\ \mu m.$$

[3] The cascade impactor is available as the Model 160 Marple-Miller Impactor from MSP Corporation, Minneapolis, MN. The inhaler should be connected to the impactor via the induction port, shown in *Figure 4a*.

General Procedure—Perform the test using *Apparatus 2* at the airflow rate, ~~*Q*~~,

■Q_{out}■1S (*USP27*)
determined earlier, during testing for ~~*Uniformity of Dosage Units*~~

■*Delivered-Dose Uniformity*,■2S (*USP26*)
provided ~~*Q*~~,

■Q_{out}■1S (*USP27*)
is less than or equal to 100 L per minute. [NOTE—If ~~*Q*~~,

■Q_{out}■1S (*USP27*)
is greater than 100 L per minute, use an airflow rate of 100 L per minute.] Connect the apparatus to a flow control system that is based upon critical (sonic) flow as specified in *Figure 5* (see also *Table 2*).

Table 2. Component Specifications for *Figure 5*

Code	Item	Description	Dimensions
A	Connector	(e.g., short metal coupling with low diameter branch to P3)	$\geq$ 8-mm ID
B	Vacuum tubing	(e.g., silicon tubing with an outside diameter of 14 mm and an internal diameter of 8 mm)	8 $\pm$ 0.5-mm ID $\times$ 50 $\pm$ 10-cm length
C	Two-way solenoid valve[a]	See *Figure 5*	Internal diameter orifice of 9.5 mm and a C_v = 1.8[a], minimal resistance to airflow and a response time <100 milliseconds.
D	Vacuum pump[b]	See *Figure 5*	Pump must be capable of drawing the required flow rate through the assembled apparatus with the dry powder inhaler in the mouthpiece adapter. Connect the pump to the solenoid valve using short and wide ($\geq$ 10-mm ID) vacuum tubing and connectors to minimize pump capacity requirements.
E	Timer[c]	See *Figure 5*	The timer switches current directly to the solenoid valve for the required duration.
P2, P3	pressure measurements		Determine under steady-state flow conditions with an absolute pressure transducer.
F	Flow control valve[d]	See *Figure 5*	Adjustable regulating valve with maximum $C_v \geq 1$.

[a] An example being ASCO product number 8030G13 (Automatic Switch Company, 60 Hanover Road, Florham Park, NJ 07932) or equivalent. See also *Footnote h* in Table 1.
[b] Gast product type 1023, 1423, or 2565 (Gast Manufacturing Inc., PO Box 97, Benton Harbor, MI 49022) or equivalent.
[c] An example being Eaton Product number 45610-400 (Eaton Corporation, Automotive Products Division, 901 South 12th Street, Watertown, WI 53094) or equivalent.
[d] Parker Hannifin type 8FV12LNSS, or equivalent (Parker Hannifin plc, Riverside Road, Barnstable, Devon EX31 1NP, UK). See also *Footnote h* in Table 1.

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Table 3. Component Units of Multistage Liquid Impinger (see *Figure 8*)

Code[1]	Item	Description	Dimensions[2]
A,H	Jet tube	Metal tube screwed onto partition wall sealed by gasket (C), polished inner surface	see *Figure 8a*
B,G	Partition wall	Circular metal plate, diameter	120
		Thickness	see *Figure 8a*
C	Gasket	e.g., PTFE	to fit jet tube
D	Impaction plate	Porosity O sintered-glass disk,	
		Diameter	see *Figure 8a*
E	Glass cylinder	Plane polished cut glass tube	
		Height, including gaskets	46
		Outer diameter	100
		Wall thickness	3.5
		Sampling port (F) diameter	18
		Stopper in sampling port	ISO 24/25
J	Metal frame	L-profiled circular frame with slit	
		Inner diameter	to fit impaction plate
		Height	4
		Thickness of horizontal section	0.5
		Thickness of vertical section	2
K	Wire	Steel wire interconnecting metal frame and sleeve (two for each frame)	
		Diameter	1
L	Sleeve	Metal sleeve secured on jet tube by screw	
		Inner diameter	to fit jet tube
		Height	6
		Thickness	5
M	Gasket	e.g., silicone	to fit glass cylinder
N	Bolt	Metal bolt with nut (six pairs), length	205
		Diameter	4
P	O-ring	Rubber O-ring, diameter × thickness	66.34 × 2.62
Q	O-ring	Rubber O-ring, diameter × thickness	29.1 × 1.6
R	Filter holder	Metal housing with stand and outlet	see *Figure 8b*
S	Filter support	Perforated sheet metal, diameter	65
		Hole diameter	3
		Distance between holes (center-points)	4
T	Snap-locks		
U	Multi-jet tube	Jet tube (H) ending in multijet arrangement	see inserts *Figure 8a*
V	Outlet	Outlet and nozzle for connection to vacuum	Internal diameter $\geq$ 10 *(Figure 8b)*

[1] See *Fig. 8*.
[2] Measurements in mm unless otherwise stated.

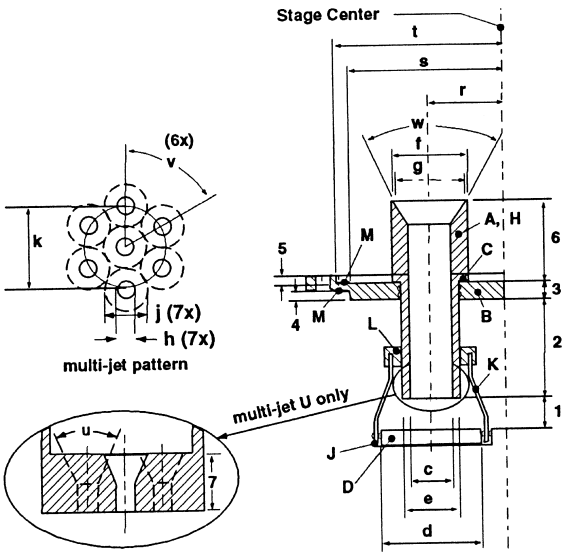

Fig. 8a. Apparatus 4: Details of jet tube and impaction plate. Inserts show end of multi-jet tube U leading to Stage 4. (See *Table 4* for dimension specifications.)

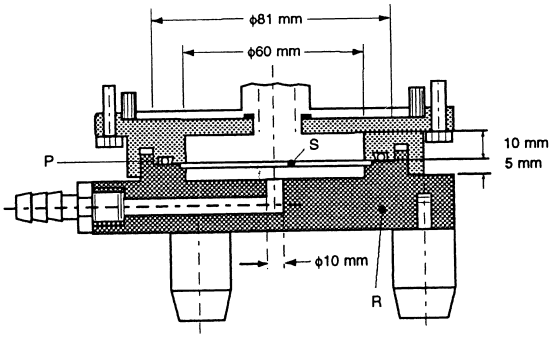

Fig. 8b. Apparatus 4: Expanded view of Stage 5. (See *Table 3* for component specifications.)

Under steady flow conditions, at the appropriate volumetric airflow rate through the entire apparatus, ensure that critical (sonic) flow occurs in the flow control valve by determining the individual values for absolute pressure, P2 and P3, so that their ratio P3/P2 is less than or equal to 0.5. ~~If not demonstrated to be unnecessary, coat~~

■Coat■1S (*USP27*) the particle collection surface of each of the stages of the cascade impactor to ensure that particles that have impacted on a given stage are not re-entrained in the flowing airstream, ~~This may be achieved by coating collection surfaces with silicone fluid, glycerol, or other adhesive substances.~~

■unless this has been shown to be unnecessary.■1S (*USP27*) Analyze the data as directed under *Data Analysis*.

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Table 4. Apparatus 4: Dimensions[1] of Jet Tube with Impaction Plate *(see Figure 8a)*

Type	Code[2]	Stage 1	Stage 2	Stage 3	Stage 4	Filter (Stage 5)
Distance	1	9.5 (–.0, +.5)	5.5 (–.0, +.5)	4.0 (–.0, +.5)	6.0 (–.0, +.5)	n.a.
Distance	2	26	31	33	30.5	0
Distance	3	8	5	5	5	5
Distance	4	3	3	3	3	n.a.
Distance	5	0	3	3	3	3
Distance	6[3]	20	25	25	25	25
Distance	7	n.a.	n.a.	n.a.	8.5.	n.a.
Diameter	c	25	14	8.0 (±.1)	21	14
Diameter	d	50	30	20	30	n.a.
Diameter	e	27.9	16.5	10.5	23.9	n.a.
Diameter	f	31.75 (–.05, +.00)	22	14	31	22
Diameter	g	25.4	21	13	30	21
Diameter	h	n.a.	n.a.	n.a.	2.70 (±.05)	n.a.
Diameter	j	n.a.	n.a.	n.a.	6.3	n.a.
Diameter	k	n.a.	n.a.	n.a.	12.6	n.a.
Radius[4]	r	16	22	27	28.5	0
Radius[4]	s	46	46	46	46	n.a.
Radius[4]	t	n.a.	50	50	50	50
Angle	w	10°	53°	53°	53°	53°
Angle	u	n.a.	n.a.	n.a.	45°	n.a.
Angle	v	n.a.	n.a.	n.a.	60°	n.a.

[1] Measurements in mm with tolerances according to ISO 2768-m, unless otherwise stated.
[2] See *Figure 8a*.
[3] Including gasket.
[4] Relative centerline of stage compartment.
n.a.: not applicable.

Apparatus 3 for Dry Powder Inhalers—
Design—Apparatus 3 is identical to *Apparatus 1 (Figure 4)*, except that the manufacturer's preseparator is added atop Stage 0 to collect large masses of noninhalable powder prior to their entry into the impactor, and the outlet nipple, used to connect to vacuum tubing B *(Figure 5)*, is replaced with one having an internal diameter $\geq$ 8 mm. To connect the preseparator of the impactor to the induction port *(Figure 4a)*, a specially designed top for the preseparator must be used. This is shown in *Figure 7*.[4] The impactor, therefore, has eight stages, a preseparator (to collect large particulates), and an after filter. At a volumetric airflow rate of 28.3 L per minute (the nominal flow rate, Q_n), the cutoff aerodynamic diameters $D_{50,Qn}$ of Stages 0 to 7 are 9.0, 5.8, 4.7, 3.3, 2.1, 1.1, 0.7, and 0.4 µm, respectively. The after filter effectively retains aerosolized drug in the particle size range up to 0.4 µm. Connect the cascade impactor into the control system specified in *Figure 5*. Omit Stage 6 and Stage 7 from the impactor if the test flow rate, ~~Q~~,

■Q_{out},■1S (*USP27*)
used during testing for ~~*Uniformity of Dosage Units*~~

■*Delivered-Dose Uniformity*■2S (*USP26*)
was greater than or equal to 60 L per minute. ~~If necessary, coat the particle collection surface of each of the stages to ensure that particles that impact on a given stage are not re-entrained in the flowing airstream.~~

■To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary.■1S (*USP27*)

[4] The cascade impactor is available as the Andersen 1ACFM Non-Viable Cascade Impactor (Mark II) from Graseby Inc., 500 Technology Court, Smyrna, GA, 30082. The impactor is used with the preseparator.

Assemble the impactor as described in the manufacturer's literature with an after filter below the final stage to capture any fine particles that otherwise would escape from the device. Place an appropriate volume (up to 10 mL) of an appropriate solvent into the preseparator, or coat the particle collection surfaces of the preseparator to prevent re-entrainment of impacted particles. [*Caution—Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.*] Attach a molded mouthpiece adapter to the end of the induction port to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the cascade impactor are connected with airtight seals to prevent leaks.

Turn on the vacuum pump, open the two-way solenoid valve, and calibrate the airflow through the system as follows. Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Once the inhaler is positioned, discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, $T \pm 5\%$,

■as determined during testing for *Delivered-Dose Uniformity*.■1S (*USP27*)
After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, remove the inhaler from the mouthpiece adapter, and switch off the vacuum pump.

Carefully disassemble the apparatus. Using a suitable solvent, rinse the drug from the mouthpiece adapter, induction port, and preseparator, and dilute quantitatively to an appropriate volume.

Rinse the drug from each stage, and the impaction plate immediately below, into appropriately sized flasks. Quantitatively dilute each flask to an appropriate volume. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the samples. ~~The total mass of drug collected in all of the components (material balance) divided by the total number of minimum recommended doses discharged is not less than 75% and not more than 125% of the average minimum recommended dose determined during testing for *Uniformity of Dosage Units*. If the total mass is outside of this range, the test must be repeated.~~

■■2S (*USP26*)
The aerodynamic cutoff diameters of the individual stages of this device, in the airflow range between 30 and 100 L per minute, are currently ~~unknown~~

■not well established.■1S (*USP27*)
Do not use the formula in Equation 1 to calculate cutoff diameters.

Procedure—Proceed as directed in the *General Procedure* under *Apparatus 2*, except to use *Apparatus 3*.

Apparatus 4 for Dry Powder Inhalers—

■NOTE—*Apparatus 4*, the multistage liquid impinger, has a small number of stages and is used extensively outside the USA. It is provided here for the benefit of users in countries other than the USA.■1S (*USP27*)

Design—The design and assembly of *Apparatus 4* are shown in Figures *8*, *8a*, and *8b*.[5] The induction port, used to connect the device to an inhaler, is shown in *Figure 4a*. The device is a multistage liquid impinger consisting of impaction Stages 1, 2, 3, and 4 and an integral after filter (Stage 5). The collection stages of the liquid impinger (see *Figure 8* and *Table 3*) are kept moist, unlike those of traditional impactors, such as *Apparatus 1*, *2*, and *3;* wetting may produce an effect similar to coating the stages of *Apparatus 2* and *3* at certain flow rates, although this should be confirmed by demonstrating control over re-entrainment as described earlier. ~~(see *System Suitability*).~~

■■2S (*USP26*)
An impaction stage comprises an upper horizontal metal partition wall (B) through which a metal inlet jet tube (A) with its impaction plate (D) is protruding; a glass cylinder (E) with sampling port (F), forming the vertical wall of the stage; and a lower horizontal metal partition wall (G) through which a jet tube (H) connects to the lower stage. The tube into Stage 4 (U) ends in a multijet arrangement. The impaction plate (D) is secured in a metal frame (J), which is fastened by two wires (K) to a sleeve (L) secured on the jet tube (C). For more detail of the jet tube and impaction plate, see *Figure 8a*. The horizontal plane of the collection plate is perpendicular to the axis of the jet tube and centrally aligned. The upper surface of the impaction plate is slightly raised above the edge of the metal frame. A recess around the perimeter of the horizontal partition wall guides the position of the glass cylinder. The glass cylinders are sealed against the horizontal partition walls with gaskets (M) and clamped together by six bolts (N). The sampling ports are sealed by stoppers. The bottom side of the lower partition wall of Stage 4 has a concentric protrusion fitted with a rubber O-ring (P) that seals against the edge of a filter placed in the filter holder. The filter holder (R) is a basin with a concentric recess in which a perforated filter support (S) is flush-fitted. The filter holder is designed for 76-mm diameter filters. The whole impaction stage assembly is clamped onto the filter holder by two snap locks (T). The impinger is equipped with an induction port *(Figure 4a)* that fits onto the Stage 1 inlet jet tube. A rubber O-ring on the jet tube provides an airtight connection to the induction port. An elastomeric mouthpiece adapter to fit the inhaler being tested provides an airtight seal between the inhaler and the induction port.

At a volumetric airflow rate of 60 L per minute (the nominal flow rate, Q_n), the cutoff aerodynamic diameters $D_{50,Qn}$ of Stages 1 to 4 are 13.0, 6.8, 3.1, and 1.7 µm, respectively. The after filter effectively retains aerosolized drug in the particle size range up to 1.7 µm. Ensure that *Apparatus 4* is clean and free of drug solution from any previous tests. Place a 76-mm diameter filter in the filter stage, and assemble the apparatus. Use a low pressure filter capable of quantitatively collecting the passing drug aerosol, which also allows a quantitative recovery of the collected drug. Set up *Apparatus 4* using the control system as specified in *Figure 5*. Attach the induction port *(Figure 4a)* and mouthpiece adapter to produce an airtight seal between the inhaler mouthpiece and the induction port. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Ensure that the various stages of the apparatus are connected with airtight seals to prevent leaks. Turn on the vacuum pump, open the two-way solenoid valve, and calibrate the airflow through the system as follows. Connect a flowmeter, calibrated for the volumetric flow rate leaving the meter, tothe induction port. Adjust the flow-control valve to achieve a steady flow through the system at the required rate, ~~Q, so that Q~~

■Q_{out}, so that Q_{out}■1S (*USP27*)
is within ± 5% of the value determined during testing for ~~*Uniformity of Dosage Units.*~~

■*Delivered-Dose Uniformity.*■2S (*USP26*)
Ensure that critical flow occurs in the flow-control valve, at the value of ~~Q~~

■Q_{out}■1S (*USP27*)
to be used during testing, using the following procedure. With the inhaler in place, and the intended flow running, measure the absolute pressure on both sides of the flow-control valve (P2 and P3 in *Figure 5*). A ratio of P3/P2 ≤ 0.5 indicates critical flow. Switch to a more powerful pump, and remeasure the test flow rate if P3/P2 > 0.5. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens that valve for the same duration, *T*, as used during testing for ~~*Uniformity of Dosage Units.*~~

■*Delivered-Dose Uniformity.*■2S (*USP26*)
Dispense 20 mL of a solvent, capable of dissolving the drug, into each of the four upper stages of *Apparatus 4*, and replace the stoppers. [*Caution—Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.*] Tilt the apparatus to wet the stoppers, thereby neutralizing their electrostatic charge. Adjust the timer controlling the operation of the two-way solenoid valve so that it opens the valve for the same duration, *T*, as used during testing for ~~*Uniformity of Dosage Units*~~.

■*Delivered-Dose Uniformity.*■2S (*USP26*)
Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, T ± 5%. After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to

[5] The five-stage impinger is available from Copley Instruments, plc, Nottingham, UK. The inhaler should be connected to the impactor via the induction port, shown in Fig. 4 and 4a.

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the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Dismantle the filter stage of *Apparatus 4*. Carefully remove the filter, and extract the drug with solvent. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume. Rinse the inside of the inlet jet tube to Stage 1 *(Figure 8)*, allowing the solvent to flow into the stage. Rinse the drug from the inner walls and the collection plate of each of the four upper stages of the apparatus, into the solution in the respective stage, by tilting and rotating the apparatus, while ensuring that no liquid transfer occurs between the stages. Using the method of analysis specified in the individual monograph, determine the mass of drug collected in each of the six volumes of solvent. Ensure that the method corrects for possible evaporation of the solvent during the test. This may involve the use of an internal standard (of known original concentration in the solvent and assayed at the same time as the drug) or the quantitative transfer of the liquid contents from each of the stages, followed by dilution to a known volume. ~~The total mass of drug collected in all of the components (material balance) divided by the total number of minimum recommended doses discharged is not less than 75%, and not more than 125% of the average minimum recommended dose determined during testing for *Uniformity of Dosage Units*. If the total mass is outside of this range, the test must be repeated.~~

■■2S (*USP26*)
Determine the cutoff diameters of each of the individual stages of the impactor, at the value of ~~*Q*~~

■$Q = Q_{out}$■1S (*USP27*)
employed in the test by the formula:

$$D_{50,Q} = D_{50,Qn}\,(Qn/Q)^{1/2},$$

where $D_{50,Q}$ is the cutoff diameter at the flow rate, Q, employed in the test, and the subscript, n, refers to the nominal values determined when Q_n equals 60 L of air per minute. Thus, when Q equals 40 L of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,40\mathrm{LPM}} = 6.8\ \mu\mathrm{m} \times (60/40)^{1/2} = 8.3\ \mu\mathrm{m}.$$

Procedure—Proceed as directed in the *General Procedure* under *Apparatus 2*, except to use *Apparatus 4*.

■Apparatus 5 for Dry Powder Inhalers

Design—The design and assembly of *Apparatus 5*[6] are shown in *Figures 9*, *9a*, *9b*, *9c*, and *9d*. The induction port, used to connect the device to an inhaler, is shown in *Figure 4a*. The device is a cascade impactor with seven stages and a micro-orifice collector (MOC). Over the design flow-rate range of 30 to 100 L per minute, the 50% efficiency cutoff diameters of the stages (D_{50} values) range between 0.24 μm to 11.7 μm, evenly spaced on a logarithmic scale. In the design flow-rate range, there are always at least five stages with D_{50} values between 0.5 μm and 6.5 μm. The collection efficiency curves for each stage are sharp and minimize overlap between stages.

The impactor layout has removable impaction cups with all the cups in one plane (*Figures 9–9c*). There are three main sections to the impactor: the bottom frame that holds the impaction cups, the seal body that holds the jets, and the lid that contains the interstage passageways (shown in *Figures 9–9b*). Multiple nozzles are used at all but the first stage (*Figure 9c*). The flow passes through the impactor in a sawtooth pattern.

Stage mensuration is performed periodically together with confirmation of other dimensions critical to the effective operation of the impactor. Critical dimensions are provided below in *Table 5*.

[6] The cascade impactor is available as the Next Generation Pharmaceutical Impactor from MSP Corporation, Minneapolis, MN.

Table 5. Critical Dimensions for the Next Generation Pharmaceutical Impactor

Description	Dimension (mm)
Preseparator (dimension a—see *Figure 9d*)	12.80 ± 0.05
Stage 1[1] Nozzle diameter	14.30 ± 0.05
Stage 2[1]Nozzle diameter	4.882 ± 0.04
Stage 3[1] Nozzle diameter	2.185 ± 0.02
Stage 4[1] Nozzle diameter	1.207 ± 0.01
Stage 5[1] Nozzle diameter	0.608 ± 0.01
Stage 6[1] Nozzle diameter	0.323 ± 0.01
Stage 7[1] Nozzle diameter	0.206 ± 0.01
MOC [1]	0.070 (nominally 0.065 to 0.072)
Cup Depth (Dimension b—see *Figure 9b*)	14.625 ± 0.10
Collection cup surface roughness	0.5 to 2 μm
Stage 1 Nozzle to seal body distance [2]—dimension c	0 ± 0.14
Stage 2 Nozzle to seal body distance [2]—dimension c	5.186 to 5.286
Stage 3 Nozzle to seal body distance [2]—dimension c	8.415 to 8.475
Stage 4 Nozzle to seal body distance [2]—dimension c	11.349 to 11.409
Stage 5 Nozzle to seal body distance [2]—dimension c	13.146 to 13.206
Stage 6 Nozzle to seal body distance [2]—dimension c	13.969 to 14.029
Stage 7 Nozzle to seal body distance [2]—dimension c	13.970 to 14.030
MOC Nozzle to seal body distance [2]—dimension c	14.470 to 14.530

[1] See *Figure 9c.*
[2] See *Figure 9b.*

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In routine operation, the seal body and lid are held together as a single assembly. The impaction cups are accessible when this assembly is opened at the end of an inhaler test. The cups are held in a support tray, so that all cups can be removed from the impactor simultaneously by lifting out the tray. The impactor is ready for another test as soon as another tray of cups is inserted and the lid is closed.

A metal induction port with internal dimensions identical to those defined in *Figure 4a* is connected to the impactor inlet. When necessary, with dry powder inhalers, a preseparator can be added to avoid overloading the first stage. This preseparator connects between the induction port and the impactor. A suitable mouthpiece adapter is used to provide an airtight seal between the inhaler and the induction port.

At a volumetric airflow rate of 60 L per minute (the assigned reference flow rate for cutoff-diameter calculations, Q_n), the cutoff-aerodynamic diameters $D_{50,Qn}$ of Stages 1 to 7 are 8.06, 4.46, 2.82, 1.66, 0.94, 0.55 and 0.34 µm, respectively. The apparatus contains a terminal micro-orifice collector (MOC) that for most formulations may eliminate the need for a final filter as determined by method validation. The MOC is an impactor nozzle plate and collection cup. The nozzle plate contains, nominally, 4032 jets, each a nominal 70 µm in diameter. Most particles not captured on Stage 7 of the impactor will be captured on the cup surface below the MOC. (For impactors operated at 60 L per minute, the MOC is capable of collecting 80% of 0.14-µm particles). For formulations with a significant fraction of particles not captured by the MOC, there is an optional filter holder that can replace the MOC or be placed downstream of the MOC containing a suitable after-filter (glass fiber is often suitable).

Procedure—Assemble the apparatus with the preseparator (*Figure 9d*), unless experiments have shown that its omission does not result in increased interstage drug losses (>5%) or particle re-entrainment, in which case the preseparator may be omitted.

Place fresh cups into the apertures in the cup tray. To ensureefficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Insert the cup tray into the bottom frame, and lower into place. Close the impactor lid with the seal body attached, and operate the handle to lock the impactor together so that the system is airtight.

The preseparator may be assembled as follows: assemble the preseparator insert into the preseparator base; fit the preseparator base to the impactor inlet; add 15 mL of the solvent used for sample recovery to the central cup of the preseparator insert; place the preseparator body on top of this assembly; and close the two catches. [*Caution—Some solvents form flammable vapor-air mixtures that may be ignited during passage through a vacuum pump. Take appropriate precautions (e.g., alternative solvents, use of vapor traps, minimal pump operating times, etc.) to ensure operator safety during testing.*]

Connect a metal induction port with internal dimensions as defined in *Figure 4a* either to the impactor inlet or to the preseparator inlet atop the cascade impactor (*Figure 9d*). Place a suitable mouthpiece adapter in position at the end of the induction port so that the mouthpiece end of the inhaler, when inserted, lines up along the horizontal axis of the induction port. The front face of the inhaler mouthpiece is flush with the front face of the induction port. When attached to the mouthpiece adapter, the inhaler should be positioned in the same orientation as intended for use. Connect the apparatus to a flow system according to the scheme specified in *Figure 5*.

Unless otherwise prescribed, conduct the test at the flow rate used in the test for *Delivered-Dose Uniformity* drawing 4 L of air from the mouthpiece of the inhaler and through the apparatus. Connect a flowmeter to the induction port. Use a flowmeter calibrated for the volumetric flow leaving the meter, or calculate the volumetric flow leaving the meter (Q_{out}) using the ideal gas law. For a meter calibrated for the entering volumetric flow (Q_{in}), use the formula:

$$Q_{out} = Q_{in}P_0 / (P_0 - \Delta P),$$

where P_0 is the atmospheric pressure and ΔP is the pressure drop over the meter. Adjust the flow control valve to achieve steady flow through the system at the required rate, Q_{out} ($\pm 5\%$). Ensure that critical flow occurs in the flow-control valve by the procedure described for *Apparatus 2*. Adjust

the timer controlling the operation of the two-way solenoid valve so that it opens the valve for the same duration, *T*, as used during testing for *Delivered-Dose Uniformity*.

Prime or load the dry powder inhaler with powder for inhalation according to the labeled instructions. With the vacuum pump running and the two-way solenoid valve closed, insert the inhaler mouthpiece, held horizontally, into the induction port mouthpiece adapter. Discharge the powder into the apparatus by activating the timer and opening the two-way solenoid valve for the required duration, $T + 5\%$. After the two-way solenoid valve has closed, remove the inhaler from the mouthpiece adapter. If additional doses are required for the sample, reload the inhaler according to the labeled instructions, reinsert the mouthpiece into the mouthpiece adapter, and repeat the operation until the required number of doses have been discharged. After discharge of the last dose, switch off the vacuum pump.

Dismantle the apparatus, and recover drug for analysis as follows: remove the induction port and mouthpiece adapter from the preseparator and extract the drug into an aliquot of solvent; remove the preseparator from the impactor, without spilling the cup liquid into the impactor; seal the outlet of the preseparator with a suitable stopper; add an aliquot of drug recovery solvent, if necessary; seal the preseparator inlet with another suitable stopper; and shake and rotate the preseparator gently and slowly, to extract the active ingredient from all inner surfaces.

Open the impactor by releasing the handle and lifting the lid. Remove the cup tray, with the collection cups, and recover the active ingredient from each cup into an aliquot of solvent. Using the method of analysis specified in the individual monograph, determine the mass of drug contained in each of the aliquots of solvent.

Determine the cutoff diameters of each of the individual stages of the impactor, at the value of $Q = Q_{out}$ employed in the test by the formula:

$$D_{50,Q} = D_{50,Qn} (Q_n / Q)^X, \quad \text{(Eq. 2)}$$

where $D_{50,Q}$ is the cutoff diameter at the flow rate, Q, employed in the test, and the subscript, n, refers to the nominal or reference value for $Q_n = 60$ L of air per minute (see *Table 6*). The values for the exponent, x, are listed in *Table 6*. Thus, when $Q = 40$ L of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,40LPM} = 4.46\ \mu m \times (60 / 40)^{0.52} = 5.51\ \mu m.$$

Analyze the data as directed under *Data Analysis*.

Table 6. Cutoff Aerodynamic Diameter for Stages of *Apparatus 5* and *6*

Use Eq. 2 to calculate $D_{50,Q}$ for flow rates, Q, in the range 30 to 100 L per minute with $Q_n = 60$ L per minute.

Stage	$D_{50,Qn}$	x
1	8.06	0.54
2	4.46	0.52
3	2.82	0.50
4	1.66	0.47
5	0.94	0.53
6	0.55	0.60
7	0.34	0.67

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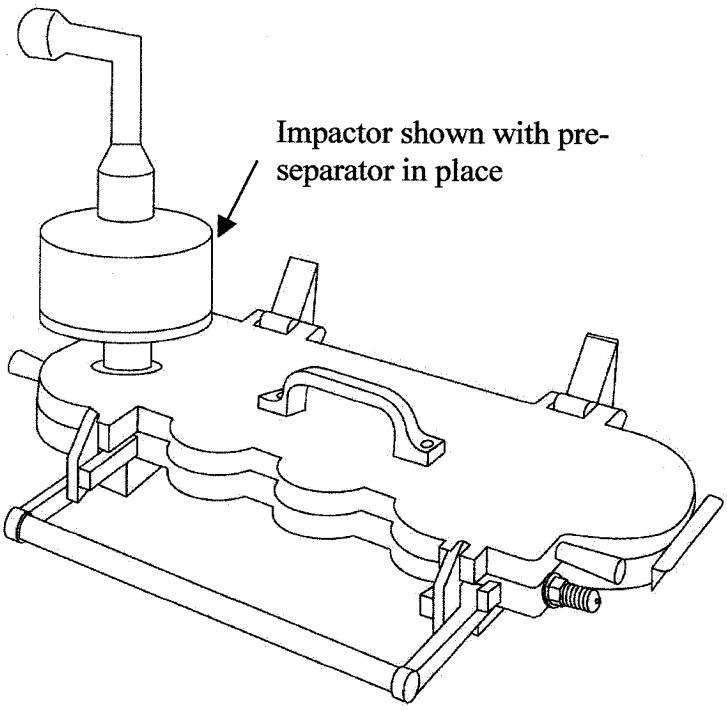

Fig. 9. Component of *Apparatus 5.*

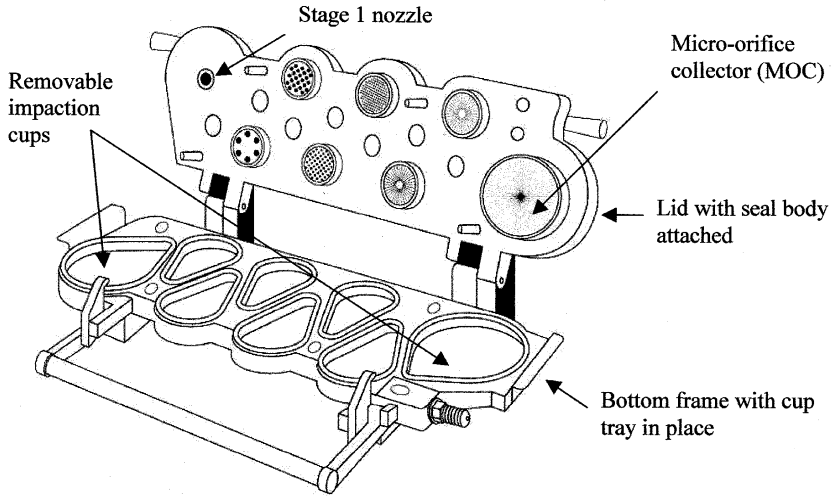

Fig. 9a. Component of *Apparatus 5.*

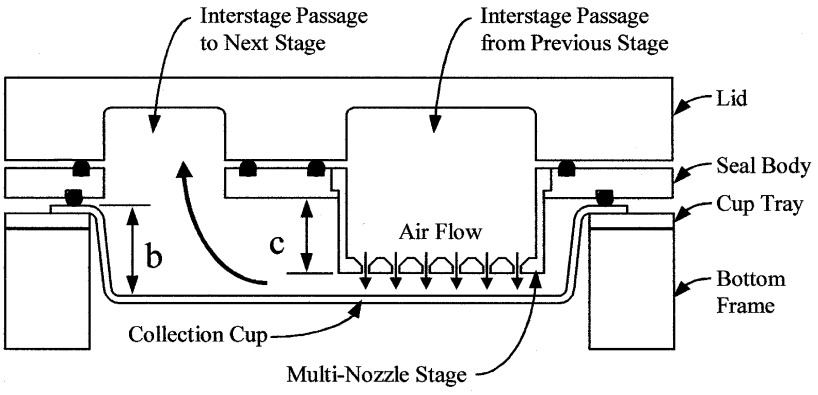

Fig. 9b. Layout of interstage passageways of *Apparatus 5.*

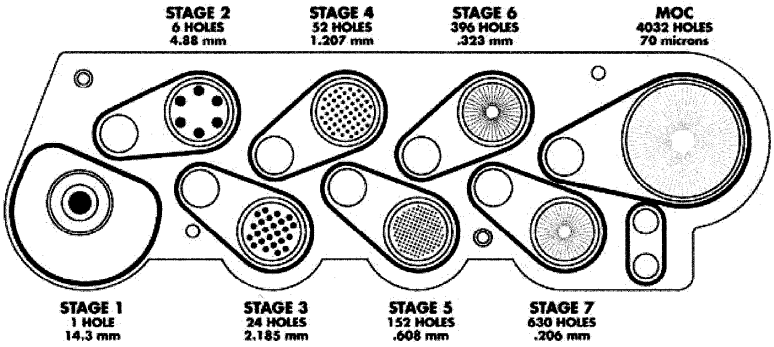

Fig. 9c. Nozzle dimensions and layout of *Apparatus 5.*

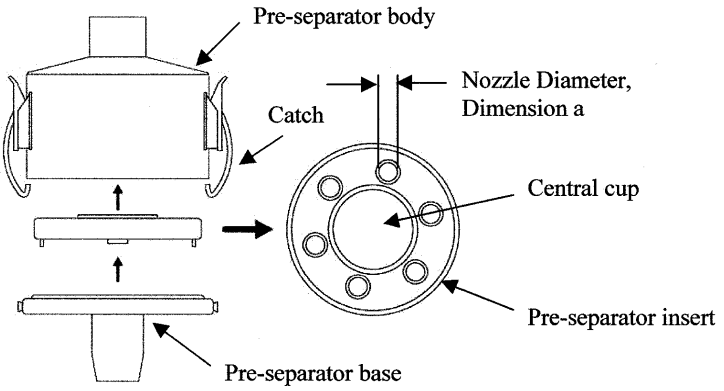

Fig. 9d. Pre-separator layout for *Apparatus 5.*

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Apparatus 6 for Metered-Dose Inhalers

Design—Apparatus 6 is identical to *Apparatus 5* (*Figures 9-9d*), except that the preseparator is not to be used. Use this apparatus at a flow rate of 30 L per minute (±5%), unless otherwise prescribed in the individual monograph.

Procedure—Assemble the apparatus without the preseparator. Place fresh cups into the apertures in the cup tray. To ensure efficient particle capture, coat the particle collection surface of each stage with glycerol, silicone oil, or other suitable liquid typically deposited from a volatile solvent, unless it has been demonstrated to be unnecessary. Insert the cup tray into the bottom frame, and lower into place. Close the impactor lid with seal body attached, and operate the handle to lock the impactor together so that the system is airtight. Connect a metal induction port with internal dimensions as defined in *Figure 4a* to the impactor inlet. Use a mouthpiece adapter that ensures that the tip of the inhaler mouthpiece is flush with the open end of the induction port. Turn on the vacuum pump to draw air through the cascade impactor, and calibrate the airflow through the system with an appropriate flowmeter attached to the open end of the induction port. Adjust the flow-control valve on the vacuum pump to achieve steady flow through the system at the required rate, and ensure that the airflow through the system is within ±5% of this flow rate. Unless otherwise prescribed in the patient instructions, shake the inhaler for 5 seconds, and discharge one delivery to waste. With the vacuum pump running, insert the mouthpiece into the mouthpiece adapter, and immediately fire the minimum recommended dose into the cascade impactor. Keep the valve depressed for a duration sufficient to ensure that the dose has been completely discharged. If additional sprays are required for the sample, wait for 5 seconds before removing the inhaler from the mouthpiece adapter, shake the inhaler, reinsert it into the mouthpiece adapter, and immediately fire the next minimum recommended dose.

Repeat until the required number of doses have been discharged. The number of minimum recommended doses discharged must be sufficient to ensure an accurate and precise determination of *Aerodynamic Size Distribution*. [NOTE—The number of minimum recommended doses is typically not greater than 10.] After the last dose has been discharged, remove the inhaler from the mouthpiece adapter. Rinse the mouthpiece adapter and induction port with a suitable solvent, and dilute quantitatively to an appropriate volume.

Dismantle the apparatus, and recover the drug for analysis as follows: remove the induction port and mouthpiece adapter from the apparatus, and recover the deposited drug into an aliquot of solvent; open the impactor by releasing the handle and lifting the lid; remove the cup tray, with the collection cups; and extract the active ingredient in each cup into an aliquot of solvent. Using the method of analysis specified in the individual monograph, determine the quantity of active ingredient contained in each of the aliquots of solvent.

Determine the cutoff diameters of each of the individual stages of the impactor, at the value of Q employed in the test by using Eq. 2 with values obtained from *Table 6*. Thus, when Q = 30 L of air per minute, the cutoff diameter of Stage 2 is given by the formula:

$$D_{50,30\text{LPM}} = 4.46\ \mu\text{m} \times (60/30)^{0.52} = 6.40\ \mu\text{m}.$$

To analyze the data, proceed as directed under *Data Analysis*.■1S (*USP27*)

Data Analysis

This section describes the data analysis required to define the *Aerodynamic Size Distribution* of the drug output from the test inhaler, after the use of *Apparatus 1*, *2*, *3*, ~~*or 4*~~

■*4, 5,* or *6.*■1S (*USP27*)
Enter the data collected from *Apparatus 1*, *2*, *3*, ~~*or 4*~~

■*4, 5,* or *6*■1S (*USP27*)
in the table of mass summaries as shown in ~~*Table 5.*~~

■*Table 7.*■1S (*USP27*)
Perform only those calculations specified in the individual monograph.

~~Table 5. Critical Dimensions for the Next Generation Pharmaceutical Impactor~~

~~Description~~	~~Dimension (mm)~~
~~Preseparator (dimension a—see *Figure 9d*)~~	~~12.80 ± 0.05~~
~~Stage 1[+] Nozzle diameter~~	~~14.30 ± 0.05~~
~~Stage 2[+] Nozzle diameter~~	~~4.882 ± 0.04~~
~~Stage 3[+] Nozzle diameter~~	~~2.185 ± 0.02~~
~~Stage 4[+] Nozzle diameter~~	~~1.207 ± 0.01~~
~~Stage 5[+] Nozzle diameter~~	~~0.608 ± 0.01~~
~~Stage 6[+] Nozzle diameter~~	~~0.323 ± 0.01~~
~~Stage 7[+] Nozzle diameter~~	~~0.206 ± 0.01~~
~~MOC[+]~~	~~0.070 (nominally 0.065 to 0.072)~~
~~Cup Depth (Dimension b—see *Figure 9b*)~~	~~14.625 ± 0.10~~
~~Collection cup surface roughness~~	~~0.5 to 2 µm~~
~~Stage 1 Nozzle to seal body distance[2]—dimension e~~	~~0 ± 0.14~~
~~Stage 2 Nozzle to seal body distance[2]—dimension e~~	~~5.186 to 5.286~~
~~Stage 3 Nozzle to seal body distance[2]—dimension e~~	~~8.415 to 8.475~~
~~Stage 4 Nozzle to seal body distance[2]—dimension e~~	~~11.349 to 11.409~~
~~Stage 5 Nozzle to seal body distance[2]—dimension e~~	~~13.146 to 13.206~~
~~Stage 6 Nozzle to seal body distance[2]—dimension e~~	~~13.969 to 14.029~~
~~Stage 7 Nozzle to seal body distance[2]—dimension e~~	~~13.970 to 14.030~~
~~MOC Nozzle to seal body distance[2]—dimension e~~	~~14.470 to 14.530~~

~~[1] See *Figure 9c.*~~
~~[2] See *Figure 9b.*~~

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■**Table 7. Table of Mass Summaries for Analyses of Metered-Dose Inhalers and Dry Powder Inhalers**

Mass	Apparatus 1		Apparatus 2		Apparatus 3[a]		Apparatus 4[b]		Apparatus 5[d]		Apparatus 6[d]	
Mouthpiece adapter	A_i	—	A_iA_i	—	A_i	—	A_i	—	A_i	—	A_i	—
Preseparator	—	—	—	—	A_P	—	—	—	A_P	—	—	—
Stage 0 of impactor	A_0	B_0	—	—	A_0	B_0	—	—	—	—	—	—
Stage 1 of impactor/ impinger	A_1	B_1	A_1	—	A_1	B_1	A_1	—	A_1	B_1	A_1	B_1
Stage 2 of impactor/ impinger	A_2	B_2	A_2	B_2	A_2	B_2	A_2	B_2	A_2	B_2	A_2	B_2
Stage 3 of impactor/ impinger	A_3	B_3	A_3	B_3	A_3	B_3	A_3	B_3	A_3	B_3	A_3	B_3
Stage 4 of impactor/ impinger	A_4	B_4	A_4	B_4	A_4	B4	A_4	B_4	A4	B_4	A_4	B_4
Stage 5 of impactor/ impinger	A_5	B_5	A_5	B_5	A_5	B_5	—	—	A_5	B_5	A_5	B_5
Stage 6 of impactor/ impinger	A_6	B_6	—	—	A_6	B_6	—	—	A_6	B6	A_6	B_6
Stage 7 of impactor/ impinger	A_7	B_7	—	—	A_7	B_7	—	—	A_7	B_7	A_7	B_7
Filter	A_F	B_F	A_F	B_F	A_F	B_F	A_F	B_F	A_F	B_F	A_F	B_F
Sums Of Masses	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c	ΣA^c	ΣB^c

[a] Stages 6 and 7 are omitted from *Apparatus 3* at airflow rates >60 L per minute.
[b] Stage 5 of *Apparatus 4* is the filter stage (see *Figure 8*).
[c] ΣA is the total drug mass recovered from the apparatus; ΣB is the mass of drug recovered from the impactor (*Apparatus 1*, *3*, *5* and *6*) or from the impactor stages beneath the uppermost stage (*Apparatus 2*, and *4*).
[d] For *Apparatus 5* and *6*, values for the drug masses AF and BF refer to collections from the MOC, and/or the after-filter if used.■1S (*USP27*)

CALCULATIONS

Fine Particle Dose and Fine Particle Fraction—Calculate the total mass, ΣA, of drug delivered from the mouthpiece of the inhaler into the apparatus. Then calculate the total mass, *R*, of drug found on the stages of the apparatus and the filter that captured the drug in the fine particle size range appropriate for the particular drug being tested. The *Fine Particle Dose* is calculated by the formula:

$$R / n,$$

where *R* is as stated above, and *n* is the number of doses discharged during the test. The *Fine Particle Fraction* that would be delivered from the inhaler is then calculated by the formula:

$$R / \Sigma A.$$

Cumulative Percentage (Cum%) of Drug Mass Less Than Stated Aerodynamic Diameter—Construct ~~*Table 6*~~

■*Table 8*■1S (*USP27*)
by dividing the mass of drug on the filter stage by ΣB ~~(see *Table 5*).~~

■(see *Table 7*).■1S (*USP27*)

Multiply the quotient by 100, and enter this number as a percentage opposite the effective cutoff diameter of the stage immediately above it in the impactor or impinger stack. For *Apparatus 2* or *4*, use Eq. 1 to calculate the stage cutoff diameters, $D_{50,Q}$, at the airflow rate, *Q*, employed during the test.

■For *Apparatus 5* and *6*, use Eq. 2 with *Table 6*.■1S (*USP27*)
For *Apparatus 1*, use the cutoff diameters quoted by the manufacturer. For *Apparatus 3*, present the data as cumulative percentages of mass on and below the stated stage, and avoid assigning values to stage cutoff diameters.

Repeat the calculation for each of the stages in the impactor or impinger stack, in reverse numerical order (largest to smallest stage number). For each stage, calculate the cumulative percentage of mass less than the stated aerodynamic diameter by adding the percentage of the mass on that stage to the total percentage from the stages below and entering the value opposite the effective cutoff diameter of the stage above it in the stack. Thus, the percentage of drug on the filter can be seen to have aerodynamic diameters less than the cutoff diameter of the stage above the filter, and the percentage on the filter plus the percentage on the stage above have diameters less than the cutoff diameter of the stage above that, and so on. Repeat the calculation for each of the remaining stages in reverse numerical order ~~(see *Table 6*).~~

■(see *Table 8*).■1S (*USP27*)

~~**Table 6. Cutoff Aerodynamic Diameter for Stages of *Apparatus 5 and 6***~~

~~Use Eq. 2 to calculate $D_{50,Q}$ for flow rates, Q, in the range 30 to 100 L per minute with Q_n = 60 L per minute.~~

~~*Stage*~~	~~D_{50,Q_n}~~	~~*x*~~
~~1~~	~~8.06~~	~~0.54~~
~~2~~	~~4.46~~	~~0.52~~
~~3~~	~~2.82~~	~~0.50~~
~~4~~	~~1.66~~	~~0.47~~
~~5~~	~~0.94~~	~~0.53~~
~~6~~	~~0.55~~	~~0.60~~
~~7~~	~~0.34~~	~~0.67~~

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■Table 8. Cumulative Percentage (Cum%) of Mass Less than the Stated Aerodynamic Diameter

	Apparatus 1		Apparatrus 2		Apparatus 3[a]		Apparatus 4[b]		Apparatus 5		Appratus 6	
Mass	Cum%[c]	D_{50}[d]	Cum%[c]	$D_{50,Q}$[d]	Cum%[c]	$D_{50,Q}$[e]	Cum%[c]	$D_{50,Q}$[d]	Cum%[c]	$D_{50,Q}$[d]	Cum%[c]	$D_{50,Q}$[d]
Filter		0.4		0.625		0.4		1.7		0.34		0.34
Stage 7	b	0.7	—	—	b	0.7	—	—	b	0.55	b	0.55
Stage 6	c	1.1	—	—	c	1.1	—	—	c	0.94	c	0.94
Stage 5	d	2.1	b	1.25	d	2.1	—	—	d	1.66	d	1.66
Stage 4	e	3.3	c	2.5	e	3.3	b	3.1	e	2.82	e	2.82
Stage 3	f	4.7	d	5.0	f	4.7	c	6.8	f	4.46	f	4.46
Stage 2	g	5.8	100	10.0	g	5.8	100	13.0	g	8.06	g	8.06
Stage 1	h	9.0	—	—	h	9.0	—	—	—	——	—	—
Stage 0	100	—	—	—	100	—	—	—	100	—	100	—

[a] Stages 6 and 7 are omitted from *Apparatus 3* at flow rates >60 L per minute; thus, values for b and c should be omitted for *Apparatus 3*, where necessary.
[b] The filter stage in *Apparatus 4* is Stage 5 (see *Figure 8*).
[c] [(mass on stage / ΣB) × 100] % + (total% of ΣB from stages below).
[d] The 50% cutoff diameter of the stage immediately above that indicated (e.g., for Stage 4, enter the cutoff diameter for Stage 3; for *Apparatus 2* or *4*, calculate as $D_{50,Q}$ from Eq. 1; for *Apparatus 5* or *6*, calculate as $D_{50,Q}$ from Eq. 2 using *Table 6*). Values entered in the Table are correct for *Apparatus 1*, *2*, *4*, *5*, and *6* only when used at 28.3, 60.0, 60.0, 60.0, and 60.0 liters per minute, respectively.
[e] The D_{50} values are only valid at a flow rate of 28.3 L per minute.■1S (*USP27*)

If necessary, and where appropriate, plot the percentage of mass less than the stated aerodynamic diameters, versus the aerodynamic diameter, $D_{50,Q}$, on log probability paper. Calculate the GSD by the equation:

$$GSD = \sqrt{\frac{Size\ X}{Size\ Y}}.$$

Use these data and/or plot to determine values for MMAD and GSD etc., as appropriate and when necessary (see *Figure 10*).

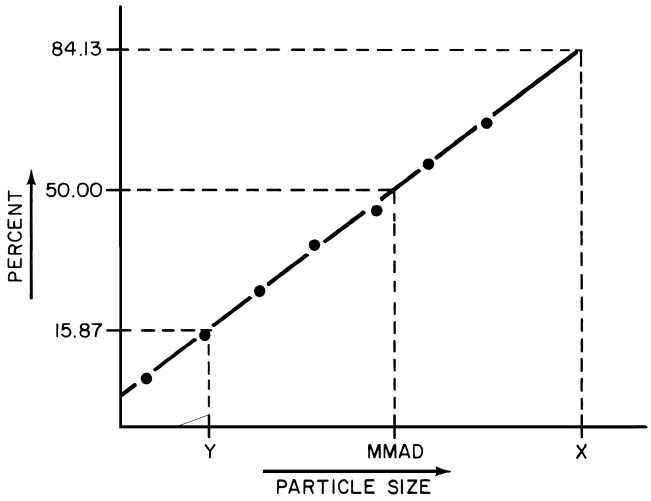

Fig. 10. Plot of cumulative percentage of mass less than the stated aerodynamic diameter versus aerodynamic diameter.

BRIEFING

⟨**621**⟩ **Chromatography,** *USP 26* page 2126, page 3008 of the *First Supplement*, and page 842 of *PF* 29(3) [May–June 2003]. The current process of including a new chromatographic reagent in *USP–NF* is by creating a new L, G, or S designation, as appropriate, numbering it, and describing the packing, phase, or support. The numbering is sequential. This process is creating some confusion between the official *USP–NF* and the proposed text in *Pharmacopeial Forum*. When a proposal is published in *Pharmacopeial Forum* that requires a new chromatographic reagent, a new numbered designation is created, and this number will be pending until the monograph that calls for this column becomes official in the next official publication, whether Supplement or the next Book. Meanwhile a designation previously proposed in *Pharmacopeial Forum* may be forwarded to the next official publication using the same numbered designation.

To avoid this confusion, henceforth, the chromatographic reagents will receive a numbered designation ONLY when the text becomes official. During the proposal period—publication in *Pharmacopeial Forum*—the new chromatographic reagent will be identified in the general test chapter *Chromatography* ⟨621⟩ by L##, G##, or S## with the title of the monograph and the brand name of the column in parentheses. In the text of the monograph that requires the new reagent, L##, G##, or S## will appear with a cross reference (see *Chromatography* ⟨621⟩). No numbers will be assigned during the proposal period.

Other revisions to this chapter include the following: Information regarding a suitable column L24 is updated. In the monograph *Paclitaxel*, packing L43 was developed for the column (TAC-1, manufactured by Whatman) that was used to develop and validate the *Related compounds, Test 1*. This column has a propyl spacer between the pentafluorophenyl groups and the silica particles. As of this date, we have not received any information from reviewers that this kind of column without the propyl spacer can be used for this test; therefore, the description of L43 is being modified to only refer to columns with a propyl spacer.

(HDQ: M. Marques) RTS—39940-1

Change to read:

CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE—Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

Packings

L1—Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to 10 µm in diameter.

L2—Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to 50 µm in diameter.

L3—Porous silica particles, 5 to 10 µm in diameter.

L4—Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

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L5—Alumina of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L6—Strong cation-exchange packing–sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to 50 µm in diameter.

L7—Octylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L8—An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, 10 µm in diameter.

L9—10-µm irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10—Nitrile groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L11—Phenyl groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L12—A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to 50 µm in diameter.

L13—Trimethylsilane chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L14—Silica gel 10 µm in diameter having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating.

L15—Hexylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L16—Dimethylsilane chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L17—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to 11 µm in diameter.

L18—Amino and cyano groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L19—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about 9 µm in diameter.

L20—Dihydroxypropane groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L21—A rigid, spherical styrene-divinylbenzene copolymer, 5 to 10 µm in diameter.

L22—A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about 10 µm in size.

L23—An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about 10 µm in size.

L24—A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to 63 µm in diameter.[5]

L25—Packing having the capacity to separate compounds with a molecular weight range from 100–5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26—Butyl silane chemically bonded to totally porous silica particles, 5 to 10 µm in diameter.

L27—Porous silica particles, 30 to 50 µm in diameter.

L28—A multifunctional support, which consists of a high purity, 100 Å, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.

L29—Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, 5 µm in diameter with a pore volume of 80 Å.

L30—Ethyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L31—A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of 8.5-µm macroporous particles having a pore size of 2000 Å and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene.

L32—A chiral ligand-exchange packing–L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to 10 µm in diameter.

L33—Packing having the capacity to separate ■dextrans■1S (*USP26*) by molecular size over a range of 4,000 to ■500,000■1S (*USP26*) Da. It is spherical, silica-based, and processed to provide pH stability.[6]

L34—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about 9 µm in diameter.

L35—A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of 150 Å.

L36—A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to 5-µm aminopropyl silica.

L37—Packing having the capacity to separate proteins by molecular size over a range of 2,000 to 40,000 Da. It is a polymethacrylate gel.

L38—A methacrylate-based size-exclusion packing for water-soluble samples.

L39—A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40—Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to 20 µm in diameter.

L41—Immobilized α_1-acid glycoprotein on spherical silica particles, 5 µm in diameter.

L42—Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, 5 µm in diameter.

L43—Pentafluorophenyl groups chemically bonded to silica particles

■by a propyl spacer,■1S (*USP27*)
5 to 10 µm in diameter.

L44—A multifunctional support, which consists of a high purity, 60 Å, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45—Beta cyclodextrin bonded to porous silica particles, 5 to 10 µm in diameter.

L46—Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, 10 µm in diameter.

L47—High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.[7]

L48—Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, 15 µm in diameter.

L49—A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to 10 µm in diameter.[8]

L50—Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm in diameter, and a surface area not less than 350 m^2 per g. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene.[9]

[5] Available as ~~Fractogel TSK HW 40F and distributed by Merck and Co.~~

■ YMC-Pack PVA-SIL manufactured by YMC Co., Ltd.■1S (*USP27*)

[6] Available as TSKgel G4000 SWXL from TosoHaas (www.tosohaas.com).

[7] Available as CarboPac MA1 and distributed by Dionex Corporation.

[8] Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.

[9] Available as OmniPac PAX-500 and distributed by Dionex Corporation.

▲L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to 10 µm in diameter.[10]
L52—A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.[11] ▲*USP26*
■L53—Weak cation-exchange resin consisting of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than 500 µEq/column. [12] ■1S (*USP26*)

■L~~53~~ ## (Alendronic Acid Tablets, PRP-X100)—An anion-exchange resin consisting of a rigid, spherical styrene-divinylbenzene copolymer with trimethylammonium groups at a loading of about 2 mEq per g, 3 to 20 µm in diameter.[14] ■1S (*USP27*)

■L~~54~~ ## (Maltose, Aminex HPX-87N)—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.[25] ■1S (*USP27*)

■L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter allowing resolution of oligosaccharides in the molecular weight range of 180 to 3000.[18] ■2S (*USP26*)

■L~~57~~ ## (Nevirapine, Supelcosil ABZ)—Spherical, porous silica gel, 3 or 5 µm in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about 6 µmoles per m^2.[19] ■1S (*USP27*)

■L~~58~~ ## (Albumin Human, TSKgel G3000 SW)—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa. It is spherical (10 µm), silica-based, and processed to provide hydrophilic characteristics and pH stability.[20] ■1S (*USP27*)

■L~~59~~ ## (Clonidine, Zorbax SB-C3)—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.[21] ■1S (*USP27*)

■L~~60~~ ## (Bethanecol Chloride, Bethanecol Chloride Tablets, IC-Pak C M/D)—A strong cation exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.[23] ■1S (*USP27*)

■L~~61~~ ## (Lycopene, Lycopene Preparation, YMC 30)—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter. ■1S (*USP27*)

Phases

G1—Dimethylpolysiloxane oil.
G2—Dimethylpolysiloxane gum.
G3—50% Phenyl-50% methylpolysiloxane.
G4—Diethylene glycol succinate polyester.
G5—3-Cyanopropylpolysiloxane.
G6—Trifluoropropylmethylpolysiloxane.
G7—50% 3-Cyanopropyl-50% phenylmethylsilicone.
G8—80% Bis(3-cyanopropyl)-20% 3-cyanopropylphenylpolysiloxane (percentages refer to molar substitution).
G9—Methylvinylpolysiloxane.
G10—Polyamide formed by reacting a C_{36} dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00:0.90:0.20.
G11—Bis(2-ethylhexyl) sebacate polyester.
G12—Phenyldiethanolamine succinate polyester.
G13—Sorbitol.
G14—Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15—Polyethylene glycol (av. mol. wt. of 3000 to 3700).
G16—Polyethylene glycol compound (av. mol. wt. about 15,000). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.
G17—75% Phenyl-25% methylpolysiloxane.
G18—Polyalkylene glycol.

[10] Available as Chiralpak AD from Chiral Technologies, Inc., 730 Springdale Drive, P.O. Box 564, Exton, PA 19341.
[11] Available as TSK IC SW Cation from TosoHaas.
[12] Available as IonPac CS14 distributed by Dionex Corporation (www.dionex.com).
[14] Available as PRP-X100 from Hamilton Company (www.hamiltoncompany.com).
[25] Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143), Group Headquarters, Bio-Rad Laboratories, 2000 Alfred Nobel Dr., Hercules, California 94547 (www.discover.bio-rad.com).
[18] Available as Superdex Peptide 10/300 GL from Amersham Biosciences (www.amershambiosciences.com).
[19] Available as Supelcosil ABZ from Supelco. (www.sigma-aldrich.com/supelco)
[20] Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05103 and 05317, respectively). (www.tosohbiosep.com)
[21] Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.-com/chem)
[23] Available as IC-Pak C M/D from Waters Corp. (www.waters.com).

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G19—25% Phenyl-25% cyanopropyl-50% methylsilicone.
G20—Polyethylene glycol (av. mol. wt. of 380 to 420).
G21—Neopentyl glycol succinate.
G22—Bis(2-ethylhexyl) phthalate.
G23—Polyethylene glycol adipate.
G24—Diisodecyl phthalate.
G25—Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and adiepoxide that is esterified with terephthalic acid. Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.
G26—25% 2-Cyanoethyl-75% methylpolysiloxane.
G27—5% Phenyl-95% methylpolysiloxane.
G28—25% Phenyl-75% methylpolysiloxane.
G29—3,3′-Thiodipropionitrile.
G30—Tetraethylene glycol dimethyl ether.
G31—Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30.
G32—20% Phenylmethyl-80% dimethylpolysiloxane.
G33—20% Carborane-80% methylsilicone.
G34—Diethylene glycol succinate polyester stabilized with phosphoric acid.
G35—A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.
G36—1% Vinyl-5% phenylmethylpolysiloxane.
G37—Polyimide.
G38—Phase G1 containing a small percentage of a tailing inhibitor.[13]
G39—Polyethylene glycol (av. mol. wt. about 1500).
G40—Ethylene glycol adipate.
G41—Phenylmethyldimethylsilicone (10% phenyl-substituted).
G42—35% phenyl-65% dimethylpolysiloxane (percentages refer to molar substitution).
G43—6% cyanopropylphenyl-94% dimethylpolysiloxane (percentages refer to molar substitution).
G44—2% low molecular weight petrolatum hydrocarbon grease and 1% solution of potassium hydroxide.
G45—Divinylbenzene-ethylene glycol-dimethylacrylate.
G46—14% Cyanopropylphenyl-86% methylpolysiloxane.
G47—Polyethylene glycol (av. mol. wt. of about 8000).
G48—Highly polar, partially cross-linked cyanopolysiloxane.

■G49—Proprietary derivatized phenyl groups on a polysiloxane backbone.[14] ■1S (*USP26*)

■G~~50~~ ## (Docosahexaenoic Acid)—Polyethylene glycol, cross-linked (av. mol. wt. of more than 20,000).[24] ■1S (*USP27*)

Supports

NOTE—Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.

S1A—Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with Na_2CO_3 flux and calcining above 900°. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane[15] to mask surface silanol groups.

S1AB—The siliceous earth as described above is both acid- and base-washed.[15]

S1C—A support prepared from crushed firebrick and calcined or burned with a clay binder above 900° with subsequent acid-wash. It may be silanized.

S1NS—The siliceous earth is untreated.

S2—Styrene-divinylbenzene copolymer having a nominal surface area of less than 50 m^2 per g and an average pore diameter of 0.3 to 0.4 μm.

S3—Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to 600 m^2 per g and an average pore diameter of 0.0075 μm.

S4—Styrene-divinylbenzene copolymer with aromatic –O and –N groups, having a nominal surface area of 400 to 600 m^2 per g and an average pore diameter of 0.0076 μm.

S5—40- to 60-mesh, high-molecular weight tetrafluorethylene polymer.

S6—Styrene-divinylbenzene copolymer having a nominal surface area of 250 to 350 m^2 per g and an average pore diameter of 0.0091 μm.

S7—Graphitized carbon having a nominal surface area of 12 m^2 per g.

S8—Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9—A porous polymer based on 2,6-diphenyl-*p*-phenylene oxide.

S10—A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11—Graphitized carbon having a nominal surface area of 100 m^2 per g modified with small amounts of petrolatum and polyethylene glycol compound.[16]

S12—Graphitized carbon having a nominal surface area of 100 m^2 per g.

[13] A suitable grade is available commercially as "SP2100/0.1% Carbowax 1500" from Supelco, Inc., Supelco Park, Bellefonte, PA 16823.

[14] A suitable grade is available commercially as "Optima Delta 3" from Machery-Nagel, Inc., 215 River Vale Road, River Vale, NJ 07675.

[24] A suitable grade is available commercially as Famewax from Restek.

[15] Unless otherwise specified in the individual monograph, silanized support is intended.

[16] Commercially available as SP1500 on Carbopack B from Supelco.

GENERAL CHAPTERS

General Information

BRIEFING

⟨**1086**⟩ **Impurities in Official Articles,** *USP 26* page 2331—See briefing under *Organic Volatile Impurities* ⟨467⟩. In addition, editorial style changes have been made.

(PA2: W. Paul) RTS—39967-2

Change to read:

DEFINITIONS

Foreign Substances

Foreign substances, which are introduced by contamination or adulteration, are not consequences of the synthesis or preparation of compendial articles and thus cannot be anticipated when monograph tests and assays are selected. The presence of objectionable foreign substances not revealed by monograph tests and assays constitutes a variance from the official standard. Examples of foreign substances include ephedrine in Ipecac or a pesticide in an oral liquid analgesic. Allowance is made in this Pharmacopeia for the detection of foreign substances by unofficial methods. (See *Foreign Substances and Impurities*, in the section *Tests and Assays*, under *General Notices and Requirements.*)

▪Residual Solvents

Residual solvents are defined as organic volatile chemicals that are used or produced in the manufacture of drug substances or excipients, or in the preparation of drug products. The solvents are not completely removed by practical manufacturing techniques. Appropriate selection of the solvent for the synthesis of a drug substance may enhance the yield or determine characteristics such as crystal form, purity, and solubility and, as such, may be a critical parameter in the synthetic process. Because there is no therapeutic benefit from residual solvents, they should be removed to the extent possible to meet product specifications, good manufacturing practices, or other quality-based requirements. Drug products should contain no higher levels of residual solvents than can be supported by safety data. A classification of residual solvents by risk assessment is presented in the *Residual Solvents Limits* section of *Organic Volatile Impurities* ⟨467⟩. Class 1 solvents should be avoided in the production of drug substances, excipients, or drug products unless their use can be strongly justified in a risk-benefit assessment.▪IS (*USP27*)

Toxic Impurities

Toxic impurities have significant undesirable biological activity, even as minor components, and require individual identification and quantitation by specific tests. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles. Based on validation data, individualized tests and specifications are selected. These feature comparison to a Reference Standard of the impurity, if available. It is incumbent on the manufacturer to provide data that would support the classification of such impurities as toxic impurities.

Concomitant Components

Concomitant components are characteristic of many bulk pharmaceutical chemicals and are not considered to be impurities in the Pharmacopeial sense. Limits on contents, or specified ranges, or defined mixtures are set forth for concomitant components in this Pharmacopeia. Examples of concomitant components are geometric and optical isomers (or racemates) and antibiotics that are mixtures. Any component that can be considered a toxic impurity because of significant undesirable biological effect is not considered to be a concomitant component.

Signal Impurities

Signal impurities are distinct from ordinary impurities in that they require individual identification and quantitation by specific tests. Based on validation data, individualized tests and specifications are selected. These feature a comparison to a reference standard of the impurity, if available.

Signal impurities may include some process-related impurities or degradation products that provide key information about the process, such as diazotizable substances in thiazides. It is incumbent on the manufacturer to provide data that would support the classification of such impurities as signal impurities rather than ordinary impurities.

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Ordinary Impurities

Ordinary impurities are those species in bulk pharmaceutical chemicals that are innocuous by virtue of having no significant, undesirable biological activity in the amounts present. These impurities may arise out of the synthesis, preparation, or degradation of compendial articles. Selections of tests and assays allow for anticipated amounts of impurities that are unobjectionable for the customary use of the article. The presence of ordinary impurities is controlled in monographs in this Pharmacopeia by including tests for *Ordinary Impurities* ⟨466⟩. Tests for *related substances* or *chromatographic purity* may also control the presence of ordinary impurities.

Unless otherwise specified in an individual monograph, estimation of the amount and number of ordinary impurities is made by relative methods rather than by strict comparison to individual Reference Standards. Nonspecific detection of ordinary impurities is also consistent with this classification.

The value of 2.0% was selected as the general limit on ordinary impurities in monographs where documentation did not support adoption of other values. This value represents the maximum allowable impact from this source of variation, when taken with the variation allowed by the composite of other Pharmacopeial tests and assays for both the bulk pharmaceutical chemical and the preparations.

Where a monograph sets limits on concomitant components, signal impurities, and/or toxic impurities, these species are not to be included in the estimation of ordinary impurities unless so stated in the individual monograph.

Related Substances

Related substances are structurally related to a drug substance. These substances may be identified or unidentified degradation products or impurities arising from a manufacturing process or during storage of a material.

Process Contaminants

Process contaminants are identified or unidentified substances (excluding related substances and water), including reagents, inorganics (e.g., heavy metals, chloride, or sulfate), raw materials, and solvents. These substances may be introduced during manufacturing or handling procedures.

BRIEFING

⟨**1136**⟩ **Packaging—Unit of Use,** page 1302 of *PF* 28(4) [July–Aug. 2002]. This general information chapter, which previously appeared in *Pharmacopeial Previews*, is now forwarded to *In-Process Revision* with the following revisions based on comments received:

- In the *Introduction* section of the chapter, including a paragraph that provides useful information on the advantages of unit-of-use packaging.
- In the section *Packaging Closure Types*, incorporating a reference to child-resistant packaging into the text of nonreclosables and a reference to the Poison Prevention Packaging Act of 1970 (PPPA) and 16 CFR 1700, which authorizes the use of special packaging to protect children from serious injury.
- In the definition of single-unit and unit-dose containers, providing clarification and adding other definitions relating to unit-of-use packaging to eliminate any contradiction to the existing definitions in the *General Notices andRequirements*.
- The advantages of bar coding on labels are outlined and its use is advocated to eliminate medication errors.

Other changes were made to clarify the intent of the chapter and to improve its readability.

(PSD: C. Okeke) RTS—39708-1

Add the following:

■⟨1136⟩ PACKAGING—UNIT OF USE

INTRODUCTION

This chapter is intended to provide guidance in the application of unit-of-use packaging. Unit-of-use packaging, when provided by the manufacturer, offers some of the following attractive advantages. (1) The ability to dispense a dosage form to a patient in the manufacturer's original container ensures that the suitability of the container has been established based on the manufacturer's stability studies. (2) Counting and repackaging of dosage units in the pharmacy is eliminated, thereby reducing the possibility of human error. (3) The pharmacist is able to affix the label for the patient onto the unit-of-use package and is free to use the manufacturer's expiration date as the beyond-use date (provided that the date is equivalent to one year or less, and that other factors were considered that might cause a different beyond-use date to be necessary). (4) The number of dosage units in a single unit-of-use package may be determined on a case-by-case basis.

DEFINITION

CONTAINER–CLOSURE SYSTEM is equivalent to a packaging system. It is the sum of the packaging components that, together, contain and protect the dosage form.

UNIT-OF-USE PACKAGE is a container–closure system that is designed to hold a specific quantity of a drug product for a specific use and that is to be dispensed to a patient without any modification except for the addition of appropriate labeling (see *General Notices and Requirements*). The packaging of a unit-of-use system may be a multiple-unit container or a ~~unit-dose~~ single-unit container. A unit of use may be a drug product in either a liquid or solid dosage form (see also the FDA *Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics*). [NOTE—The terms unit-of-use package and a unit-of-use container may be used interchangeably.]

DEBLISTERING is the process of removing medication from a blister-type container.

IMMEDIATE CONTAINER is a container that is in direct contact with the article or preparation.

MATERIALS OF CONSTRUCTION include substances used to manufacture or package components such as glass, plastics [including high-density polyethylene (HDPE), low-density polyethylene (LDPE), and polypropylene (PP)], resins, and other materials as listed in the general test chapter *Containers* ⟨661⟩ and in the FDA *Guidance for Industry on Container Closure Systems for Packaging Human Drugs and Biologics.*

TYPE OF CONTAINER FOR UNIT OF USE

Single-Unit Container

A single-unit container is a unit-dose or a single-dose container intended for either oral or parenteral use. See *General Notices and Requirements*.

UNIT-DOSE CONTAINER

A ~~single-unit container or a single-dose container,~~ unit-dose container, intended for oral use, is a container that has been packaged in the dosage regime for the course of the therapy appropriate for the drug that is to be administered.

SINGLE-DOSE CONTAINER

A single-dose container, intended for parenteral use, is a container that has been packaged in the dosage regime for the course of the therapy appropriate for the drug that is to be administered.

Multiple-Unit Container

A multiple-unit or a multiple-dose container is prepackaged in bottles or containers for injections of the drug in appropriate quantities. A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

MATERIALS OF CONSTRUCTION

Unit-of-Use Container

The Poison Prevention Packaging Act (PPPA) of 1970 authorizes the use of special packaging—child-resistant and senior-friendly packaging. Child-resistant packaging protects children from serious injury or illness from ingesting or handling hazardous household products including drugs.

Unit-of-use containers are required to be child resistant. Unit-of-use containers in child resistant single-unit containers include supported blisters, such as separate, peel,

push, and tear notch; and enclosed or in-card blisters, such as pull tabs, slide packs, etc. Unit-of-use containers in multiple unit containers include glass and plastic containers.

GLASS

~~The packaging material equivalent to the immediate container that is glass meets the glass test requirements~~ Any glass packaging material used in the immediate container should meet the glass test requirements for *Limits for Glass Types* and *Chemical Resistance—Glass Containers: Powdered Glass*, *Water Attack at 121°*, and *Arsenic* under the general test chapter *Containers* ⟨661⟩.

PLASTIC

~~The packaging material equivalent to the immediate container that is plastic meets the test requirements~~ Any plastic packaging material used in the immediate container should meet the plastic test requirements for *Plastics* in the general test chapters *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩. Depending on the type of plastic packaging material used, the packaging material meets the requirements for *Biological Tests—Plastics and Other Polymers*, *Physicochemical Tests—Plastics*, *Polyethylene Containers*, *Polyethylene Terephthalate/Polyethylene Terephthalate G*, and *Polypropylene Containers.*

The test for moisture vapor transmission may be carried out as described in the general test chapter *Containers—Permeation* ⟨671⟩ for multiple-unit and unit-dose containers.

PACKAGING CLOSURE TYPES

Reclosables and nonreclosables may be used for both solid and liquid dosage forms. Both must be packaged in compliance with the 16 CFR 1700.15 standards.

Reclosables

Reclosables are containers with suitable closures that may incorporate tamper evidence and child-resistance capabilities. Reclosables may be used for glass or plastic containers.

Nonreclosables

Nonreclosables are containers with closures that are nonreclosable such as blisters, sachets, strips, and other single-unit containers. Nonreclosables may include packs such as cold-formed foil blisters, foil strip packs, and PVC/Aclar combining multilayer materials that are thermo-formed or cold-formed foil blisters (see *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩). Nonreclosables may be child resistant depending on the intended use and place of use. Household nonreclosables are subject to the PPPA as defined in 16 CRF 1700.14. However, because of some unit-dose designs, not all unit-dose packages comply with the PPPA.

LABELING

The unit-of-use containers are labeled as such to include ~~manufacturer's lot numbers, accuracy or bar codes, and expiration dates~~ expiration dates, and in some instances, the manufacturer's lot numbers and bar codes as provided in the *Labeling* section of the *General Notices and Requirements* under *Preservation*, *Packaging*, *Storage*, *and Labeling*. Some of the advantages of having bar codes on the label include reduced medication errors, improved inventory control, and improved access to medication identity. The labeling covers information placed in the ~~pack by the manufacturer and the label added at the dispensing stage by the pharmacist.~~ container by the manufacturer (see *General Notices and Requirements*). Acceptable labeling can range from the full labeling for multiple-unit containers to

an abbreviated labeling when the container is too small to include all the text. Full labeling may also be provided on the carton if it is not present on the immediate container.

REPACKAGING AND REPROCESSING

Unit-of-use containers are reprocessed or repackaged as instructed by the manufacturer or as directed in the general test chapter *Containers* ⟨661⟩ or in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩. A unit-of-use package may not be reprocessed by a pharmacist once it has been deblistered from a unit-dose container (see *General Notices and Requirements* for application of the appropriate beyond-use date for a multiple-unit or unit-dose container). However, under current Good Manufacturing Practices (cGMPs) and tight quality controls, the manufacturer or contract repackager may repackage and reprocess unit-of-use containers.

RESPONSIBILITY OF THE DISPENSER

~~The unit of use package shall contain such label information as the following:~~

Labeling

The labeling on a unit-of-use container also includes a label added at the dispensing stage by the pharmacist. Prior to dispensing the unit-of-use package, the dispenser shall add label(s) that provide the following information:

(1) the name of the patient;

(2) the name and strength, the directions for use as prescribed by a doctor or health-care provider, and the name of the prescriber; and

(3) any storage instruction, ~~appropriate package insert, length of days of use,~~ beyond-use date, and other information as deemed appropriate by federal and state laws.

In the pharmacy setting, pharmacists are encouraged to use bar codes, in conjunction with computerized prescription orders, to confirm that the right drug is being dispensed to the right patient. Bar coding would minimize errors and create opportunity for medication traceability and accountability.

Information to Patient

Patients must be given information that applies to the specific brand of product being dispensed.

INFORMATION FROM MANUFACTURERS

The manufacturer should provide appropriate product development or stability data information that can be used to determine appropriate labeling, storage, and shipping statements that will properly inform patients and practitioners. The manufacturer may make other assurances based on product information and data on packaging and distribution arrangements. In the event that a product is not to be repackaged, the manufacturer may state so in the labeling. The manufacturer also includes labeling and information suitable for optimal handling by the practitioner and the patient. The labeling and information should be bar coded to eliminate medication error and promote medication traceability.

QUALITY CONTROL OF PACKAGING SYSTEM

The packaging system shall meet the general considerations for system suitability, protection, safety, and performance characteristics as described in the FDA *Guidance for Industry on Container Closure Systems for Packaging*

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Human Drugs and Biologics, in the general test chapter *Containers* ⟨661⟩, and in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩.■1S (*USP27*)

BRIEFING

⟨1178⟩ Good Repackaging Practices. This new general information chapter is intended to provide repackagers with guidance on applying good repackaging practices for drug products. It illustrates the distinction between repackaging a drug product under the purview of FDA and a pharmacist who repackages under the jurisdiction of the State Boards of Pharmacy. This chapter was drafted under the currently available FDA guidance documents and 21 CFR in relation to good manufacturing practices. Comments on this chapter should be addressed to Dr. Claudia Okeke.

(PSD: C. Okeke) RTS—39904-1

Add the following:

■⟨1178⟩ GOOD REPACKAGING PRACTICES

This chapter is intended to provide guidance to those engaged in repackaging of drug products in accordance with 21 CFR 10.90. A pharmacist who repackages under the state law needs to apply the principal information provided in the general information chapter *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩, and other beyond-use date references in the *General Notices and Requirements* under the *Expiration Dating* section.

This chapter provides information to any person who removes drugs from their original manufacturer's container and repacks them into a different container–closure system for resale or for distribution to hospitals or other pharmacies. It does not apply to repackaging of any *radioactive* drug products, including oral solids.

A repackager referred to here may also be a contract packager, a contract repackager, or a contract prepackager. The words ''repackager'' and ''repacker'' are the same in this text and may be used interchangeably. These functions are beyond the regular practice of a pharmacist. A repackager or prepackager is required to register with the FDA and comply with current Good Manufacturing Practices (cGMPs) regulations in 21 CFR 210 and 211.

A repackager is expected to meet the requirements of packaging practice under 21 CFR 210 through 226. Since the packaging practice relates to packaging, processing, or holding a drug product intended for administration to humans or animals, the repackager is expected to comply with regulations that relate to the sections pertaining to quality control, personnel qualifications, building and facilities, equipment, production and process controls, packaging and labeling controls, laboratory controls, batch records and reprints, distribution records, storage control records, and complaint files.

DEFINITIONS

For the purposes of this chapter repackager, contract packager, contract repackager, contract prepackager, and prepackager are defined as follows:

A REPACKAGER is one who purchases and removes a drug product from the manufacturer's market container or bulk dosage container and places the product into a different container for distribution for human or animal use. A repackager may or may not take ownership from the manufacturer. A repackager is engaged in the repackaging of drugs (see also *Packaging Practice—Repackaging a Single Solid Oral Drug Product Into a Unit-Dose Container* ⟨1146⟩ for more definitions of a repackager).

A CONTRACT PACKAGER is one who is contracted by the original drug manufacturer to package or repackage their product into a single- or multi-unit container chosen by the manufacturer. These containers should meet all the applicable requirements in this chapter, pertinent sections in general test chapters *Containers* ⟨661⟩, and *Containers—Permeation* ⟨671⟩, and comply with 21 CFR food additive requirements.

AN EQUIVALENT CONTAINER–CLOSURE SYSTEM refers to a container–closure system that yields the same, or better, moisture vapor transmission rate (MVTR), oxygen transmission, and light transmission as the original market container. These values may be determined by the repackager, or they may be obtained from the container–closure vendor for the specific container–closure system under consideration.

BEYOND-USE DATE (BUD) AND DISCARD-AFTER DATE are equivalent and are assigned using the criteria stated in the relevant section below.

EXPIRATION DATE is determined using stability studies and is not the same as beyond-use date or discard-after date.

FACILITIES

The facility in which repackaging is practiced should be operated in conformity with cGMPs. The environmental conditions during the packaging and storage operation of the drug product should comply with the *controlled room temperature* (see *General Notices*), storage in a *dry place*, and other requirements as directed by the manufacturer or supplier, especially if the drug requires storage at special temperature and humidity conditions (see *Good Storage and Shipping Practices* ⟨1079⟩).

ACQUISITION PROCESS

The repackager is expected to perform appropriate analytical testing for all pertinent specifications, such as identity and strength of each active ingredient, and any other finished product tests to establish valid analytical data. The repackager is expected to maintain records of such analyses on a batch-by-batch basis for the repackaged product that is either transferred to the repackager by the manufacturer or independently maintained by the repackager.

"Bulk" in this text refers to the quantity of either drug product or dosage form. The following criteria should be considered by the repackager upon receipt of bulk prior to repackaging.

(a) The bulk article should be distributed to the repackager by the manufacturer in accordance with all regulatory requirements and accompanied by appropriate labeling and a valid expiration date. The repackager should also receive Material Safety Data Sheets (MSDS), Certificates of Analysis, and sample market labeling, including inserts from the drug product manufacturer.

(b) The bulk article should be received intact and undamaged and in properly labeled containers with the Certificate of Analysis.

(c) The bulk article should undergo definitive organoleptic evaluations to confirm its identity (e.g., physical appearance, marking, color, and odor) and to confirm the labeling as described by the manufacturer.

(d) Records should be maintained to validate the identity and quantity of each shipment received and each lot and bar coded information of bulk article received. This record should also include the manufacturer or supplier and its lot numbers and the date of receipt.

(e) The repackager should store and maintain the bulk under storage conditions specified by the manufacturer,

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and/or as directed under *controlled room temperature* (see *General Notices*).

REPACKAGING PROCESS

The following criteria should be observed.

(a) The repackaging operations should be conducted under conditions that meet specified storage temperature definitions (see *General Notices*). Conditions of operation include maintenance of *controlled room temperature* in the area where the repackaging operation is conducted or other conditions as instructed by the manufacturer.

(b) The manufacturer should include, in the package insert or in other appropriate literature supplied to the repackager, the following information about the packaging: materials of construction of the market package, its MVTR (see ⟨671⟩), as well as oxygen transmission and light transmission characteristics in order to enable the repackager to select properly an equivalent container–closure system. If the repackager does not use a container–closure system equivalent to the manufacturer's market package, then the repackager must generate stability data for the drug product in the new container–closure system to justify the expiration date or BUD assigned.

(c) The repackaging containers are labeled with the same labeling information as the market label that is used by the manufacturer. The conditions on the labeling should meet those required under 21 CFR 201, 211.122, 211.125, and 211.130.

(d) Written procedures should be maintained to ensure that correct labels, labeling, and packaging materials are used for drug products.

(e) All requirements for repackaging of bulk products should meet 21 CFR 211.

(f) The packaging materials should meet the test requirements provided in 21 CFR in direct food additives or additives that have been approved as food contact substances. See general chapters ⟨661⟩, ⟨671⟩, and ⟨1146⟩.

LABELING

A repackager should provide appropriate labeling of the product identical to the manufacturer's approved market container. All repackaged products should be labeled with an appropriate BUD in the absence of stability data, or with an expiration date in cases where suitable stability studies, determined in CFR 211.166 (for recommended conditions see *International Conference on Harmonization ICH Q1A Stability Testing of New Drug Substances and Products*), have been performed on the product using the repackager's container. The expiration date will ensure that the products meet applicable standards of identity, strength, quality, and purity at the time of use.

EXPIRATION DATE/BEYOND-USE DATE

Expiration Date

Stability studies are performed on the drug product in the original manufacturer's containers to establish an expiration date. When a drug is repackaged into a different container, the product's expiration date is altered or interrupted.

(a) The repackager may perform stability studies on the repackaged products to establish an expiration date for the product based on scientific evaluation of the drug product in the container–closure system in which it is to be marketed.

(b) A repackager may use the manufacturer's original expiration date without additional stability testing if the drug product is repackaged into an equivalent container–closuresystem that is at least as protective as,

or more protective than, the original system and complies with criteria established for equivalency. Establishment of system equivalency means that the requirements of general test chapters ⟨661⟩ and ⟨671⟩ are met; and the specifications such as light transmission, seals, or desiccants associated with the original container–closure system, or special protective materials in which the drug product is marketed, are the same. Comparison of container–closure systems may be done through stress testing of the product after storage under exaggerated conditions of temperature and humidity.

If the repackager does not use a container–closure system equivalent to the manufacturer's market package, then the repackager must generate stability data for the drug product in the new container–closure system to justify the expiration date or BUD assigned.

(c) A repackager should not use the equivalency container–closure system criteria to repackage drug products where such products have been identified by the manufacturer to have stability problems or if the manufacturer specifically states that the product should not be repackaged using the equivalency container–closure system criteria. In this case, a repackager needs to demonstrate the stability of the drug product in the repackager's container–closure system.

(d) Establishing the expiration date in this case is applicable for unit-dose containers, multiple-unit containers, and unit-of-use container types.

Beyond-Use Date or Discard-After Date

In the absence of stability data, where a repackager repackages a product into a unit-dose or multiple-unit container without conducting appropriate stability studies to support expiration dates used, the period of use of the product is limited by the BUD for the repackaged product, which must be less than the expiration date.

UNIT-DOSE PACKAGING

For unit-dose packaging, the following criteria should be considered.

(1) The original bulk container of the drug product to be used for repackaging has not been previously opened.

(2) The contents of the original bulk drug product to be repackaged are repackaged at one time.

(3) The unit-dose container meets general test chapter ⟨671⟩ testing requirements for either Class A or Class B containers.

(4) The unit-dose container meets or exceeds the manufacturer's specification for light resistance.

(5) The conditions of storage meet the storage specifications in *General Notices* and as described in the labeling by the manufacturer of the bulk product. Where no specific storage conditions are specified, the product should be maintained at *controlled room temperature* and in a *dry place* during repackaging.

(6) The BUD used for the repackaged product does not exceed 6 months from the date of repackaging.

(7) The BUD does not exceed the manufacturer's expiration date.

(8) The BUD does not exceed 25% of the time between the date of repackaging and the expiration date shown on the manufacturer's bulk article container of the drug being repackaged.

(9) Documentation should be in place to show that the preceding criteria (items 1–8) were met. Documentation to show the type of packaging material used and the testing for these materials is also kept.

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(10) The repackager may not repackage if the manufacturer specifically states "Do not repackage." However, the repackager may affix the repackager's labeling if it is in accordance with FDA requirements and in agreement with the manufacturer of the drug product.

(11) The repackager may not use the expiration date and BUD interchangeably because they imply the presence or absence of stability testing, respectively.

MULTIPLE-UNIT PACKAGING

The *General Notices* define multiple-unit packaging as a package that contains more than one single-dosage unit. For multiple-unit packaging the following criteria should be considered in assigning a BUD.

(1) The original bulk container of drug product to be used for repackaging has not been previously opened.

(2) The contents of the original bulk drug product to be packaged are repackaged at one time.

(3) The conditions of storage meet the storage specifications in the *General Notices* and as described in the labeling of the manufacturer's bulk product. Where no specific storage conditions are specified, the product should be maintained at *controlled room temperature* and in a *dry place* during repackaging.

(4) The type of container used for repackaging should be the same type used by the manufacturer as the market container, and the product container should comply with the requirements for containers as directed under general test chapter *Containers* ⟨661⟩, as well as the requirements of 21 CFR for food additives, or be an approved food contact substance. For example, if the manufacturer packages in glass, the repackager should repackage in glass of the same type used by the manufacturer or in chemical-resistant glass containers.

(5) Where the original container is a material other than glass or high density polyethylene (HDPE), the repackager may use a container demonstrated to be equivalent to, or exceed, the protective properties of the manufacturer's multiple-unit market container when performing the applicable tests as described in general test chapters ⟨661⟩ and ⟨671⟩.

(6) Where the original container is polyethylene, the repackager may repackage in a chemical-resistant glass container or a polyethylene container. These containers should meet the appropriate tests and specifications in 21 CFR and general test chapters ⟨661⟩ and ⟨671⟩.

(7) The container meets or exceeds the test results of the manufacturer's multiple-unit market container for light transmission.

(8) The container meets or exceeds the manufacturer's container in special protective features: methods used to prevent leaching of container materials or the use of desiccants to maintain low moisture content. [NOTE—Desiccants should always be packaged on top of the drug product.]

(9) The container meets or exceeds the manufacturer's container test results for "tight" as provided in general test chapters ⟨661⟩ and ⟨671⟩.

(10) For all products, if the repackager uses a container that is equivalent in MVTR to the manufacturer's container or one that has a higher barrier, then the BUD should be 12 months or the manufacturer's expiration date, whichever is less. (See ⟨1146⟩ for description of low- and high-barrier packaging.)

(11) The repackager may not repackage the original bulk container of drug product if the manufacturer specifically states "Do not repackage." However, the repackager may affix the repackager's labeling if this is in accordance with FDA requirements or the specifications of the drug product manufacturer.

MINIMUM REQUIREMENTS

(a) A repackager is expected to comply with cGMPs and 21 CFR 211.170(b) for retained samples of repackaged drug products. Any alteration or manipulation of the repackaging process should be documented in accordance with the requirements in 21 CFR 211.

(b) A repackager is expected to repack penicillins, or products such as penicillins, in facilities separate from those facilities used for drug products as described in 21 CFR 211.42 and 21 CFR 211.46.

SHIPPING AND DISTRIBUTION

For products identified by the manufacturer as moisture- and temperature-sensitive, the repackager must follow the specifications provided by the manufacturer during repackaging, shipping, and distribution.

(a) A repackager may not repackage a moisture- and temperature-sensitive product if the manufacturer so instructs, except if the repackager is only altering the labeling in accordance with FDA requirements.

(b) The repackaging container should show the equivalent or better, in protective properties, than the manufacturer's original container. For moisture-sensitive products, a higher-barrier container should be used for repackaging.

(c) The repackager should have proper documentation in place to show the equivalency in protection of the container used.

(d) The storage and handling of the drug product should meet the conditions specifically instructed by the manufacturer of the product.

(e) The repackager should label the container"Contains moisture-sensitive product."

For all other products, the repackager should follow the same guidelines provided in *Good Storage and Shipping Practices* ⟨1079⟩ [To come] that are applicable to a manufacturer.■1S (*USP27*)

BRIEFING

⟨1265⟩ Written Prescription Drug Information—Guidelines, page 1538 of *PF* 28(5) [Sept.–Oct. 2002]. Based on comments received from the proposal in 28(5), additional revisions are made to clarify the intent of this general information chapter.

(PSD: C. Okeke) RTS—39716-1

Add the following:

■⟨1265⟩ WRITTEN PRESCRIPTION DRUG INFORMATION—GUIDELINES

The purpose of these guidelines—comprising format, content, and accessibility of prescription drug leaflets—is to help ensure that leaflets are useful. In this context, useful means that recipients receive, understand, and are motivated to apply written information about their medicines to achieve maximum benefit and minimize harm. Dispensers, prescribers, and health-care providers who counsel patients about their medicines are intended to be the primary audience for these guidelines.

FORMAT GUIDELINES

1. Group all information from the same category, using brief, clear titles and bullets or subheadings as needed. Avoid symbols and subheadings not directly connected to the information they mark.
2. Be consistent in the placement and labeling of categories of information in all leaflets.
3. Provide information at the sixth-grade reading level or below, if possible (never above eighth-grade level). Do

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not exclude information to achieve a lower reading level.

4. Use simple, common, accurate terms (for example, use ''noise in the ears'', not ''tinnitus'').
5. Use direct language that avoids words with opposite meanings (for example, use ''decrease blood pressure'', not ''increase low blood pressure effect'').
6. Provide reasons for instructions (for example, ''take with food to avoid upset stomach'').
7. Emphasize the most important information. Clearly distinguish warnings from instructions or from other text that may be misinterpreted as warnings.
8. Accompany each pictogram, if used, with corresponding text placed close to the pictogram. Use the simplest pictograms possible. For pictograms intended to prompt patients to ask questions or inform health-care providers, add text such as ''Tell Doctor'' or ''Ask Pharmacist''.
9. Make text readable by using 12-point or larger type, both uppercase and lowercase letters, an easy-to-read font (for example, a ~~sans~~ serif font), and adequate space between lines and paragraphs. To call attention to important information, use a larger, boldface type.
10. Evaluate format by performing tests of readability, comprehension, memory, problem solving, and behavioral efficacy and intention, using representative samples of the target population.

CONTENT GUIDELINES

1. Provide enough detail to facilitate correct use, achieve maximum benefit, and minimize harm including a statement that identifies activities (such as driving or sunbathing) that the patient should avoid.
2. Write text that is unbiased in content and tone and scientifically accurate. The uses described should be consistent with FDA-approved labeling or otherwise permitted by FDA, or should appear in federally recognized drug compendia. Distinguish unlabeled from labeled use. ~~For labeled use, state the date on which it was approved.~~
3. For drugs sold under a brand name, provide both brand and generic names and include a pronunciation guide for each.
4. Describe the drug and its dosage form. Include indications and contraindications, specific directions for use, what to do if a dose is missed, and what to do in the event of an overdose or poisoning.
5. Do not use abbreviations.
6. Indicate the intended type of benefit (for example, ''cure'', ''prevention'', ''to help relieve symptoms''). Indicate how—and how soon—the patient should recognize the benefit and what to do if none is observed.
7. Give a balanced evaluation of risks and benefits.
8. List side effects, in order of severity, ~~with estimated frequency and action to be taken if one or more occur~~ such as ''serious,'' ''most common,'' and other similar type groupings. It may not be appropriate to provide sufficient detail for the patient to be able to monitor serious or ~~frequently occurring~~ common side effects. ~~If no side effects are known, say so.~~ Provide guidance to consult the doctor or pharmacist, and indicate that all the side effects are not listed.
9. List ~~drug-drug, drug-food, drug-lab test, and drug-disease interactions. If no such interactions are known, say so. If appropriate, include botanicals, dietary supplements, and over-the-counter medicines, as well as other prescription medicines. If known, include estimated severity of interactions (mild, moderate, or severe). one or two most important interactions, as described earlier.~~ sufficiently specific and comprehensive information

that includes the provision of all important risk information. Patients should be advised to be sure to inform the provider about all the medicines they are taking.

10. Indicate the potential for therapeutic duplication if the drug is available under multiple names or over-the-counter, or if the active ingredient is contained in other products.
11. If known, include a statement concerning the safety of use in the presence of other conditions and during pregnancy or breast-feeding. Direct affected patients to discuss their condition with health-care providers. If the safety of use during pregnancy or breast-feeding has not been established, say so.
12. State whether safety and efficacy have been established in pediatric, geriatric, and other special populations. ~~and, if so, for what ages and doses.~~ Patients should be encouraged to discuss with their health-care provider any recommendations for dosage adjustment.
13. Illustrate information with diagrams when appropriate. Label the diagram components (for example, device parts) if they are not obvious. The words on the label should be prominently placed thereon with such conspicuousness and in such terms as to render them likely to be read and understood by the ordinary individual under customary conditions of purchase and use.
14. Include the following:
    ~~a. a warning to keep out of the reach of young children~~
    ~~b. a statement about the importance of adhering to dosing instructions~~
    ~~c.~~ a. a statement that the product is to be used only by the person for whom it was prescribed,
    ~~d.~~ b. storage information,
    ~~e.~~ c. a completeness disclaimer advising the patient to discuss this issue with the health-care provider,
    ~~f. a direction to check the expiration or beyond use date~~
    ~~g.~~ d. the publisher of the leaflet and the date the leaflet was developed or revised,
    ~~h.~~ e. sources of in-depth information and answers to questions, and
    ~~i.~~ f. other relevant general statements.
15. The patient should be advised about risks of developing dependence on, or tolerance to, the medications.

ACCESSIBILITY GUIDELINES

1. Write text that is relevant to the intended use of the drug.
2. Design the leaflets to be easy to recognize, consistent in format, and easy to store and retrieve.
3. Supplement the leaflets with oral counseling of patients, including children, the elderly, and caregivers.
4. Include a statement asking the patient to reread the leaflet.
5. Distribute the leaflets with all prescription medicines to consumers (namely, persons independently responsible for any aspect of medicine use or for giving medicines to others).
6. Produce leaflets in Spanish, ~~as well as in English;~~ English, or other languages; and establish criteria for producing them in other languages and for special populations (for example, children, visually handicapped, etc.). [NOTE—Ideally, prescription drug information leaflets would be customized for the patient's condition and for other relevant information (for example, gender, age, or physical limitations), and would be available in the patient's primary language. Currently, such customization is neither feasible nor practical, but it remains a goal.]■IS (*USP27*)

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REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Acetaldehyde, *USP 26* page 2462. Throughout the years, several members of the staff at USP have managed the *Reagents, Indicators, and Solutions* section of the *USP–NF*, adding or modifying single entries, but never treating this section as a whole document. Therefore, an extensive revision of this section, which includes *Reagent Specifications* and *Reagent Footnotes*, is proposed in this *PF* to make the information more consistent and user-friendly. Some obsolete reagents and their respective footnotes were deleted. Some specifications were, as much as possible, harmonized with the American Chemical Society (ACS) Reagent Specifications. Also, the contact information for possible suppliers was updated. Following is a list of all the reagent specifications affected by this revision.

Acetyl Chloride
Alum
Alumina, Activated
4-Amino-3-hydroxy-1-naphthalenesulfonic Acid
Ammonia Detector Tube
Ammonia Water, Stronger
Arsenic Trioxide
Benzoic Acid
7 Percent Bovine Serum Albumin Certified Standard
Butyl Acetate, Normal
Butyl Alcohol
Butyl Alcohol, Tertiary
4-(Butylamino)benzoic Acid
n-Butylboronic Acid
Calcium Acetate
Calcium Carbonate
Calcium Chloride, Anhydrous
Carbon Dioxide Detector Tube
Carbon Monoxide Detector Tube
Casein
Cation-exchange Resin, Styrene-Divinylbenzene, Strongly Acidic
Ceric Ammonium Sulfate
Chloramine T
Chlorine Detector Tube
p-Chloroaniline
Chlorobenzene
Chloroform, Alcohol-free
Chromatographic Reagents
Chromotropic Acid
Cobaltous Acetate
Compactin
Cupric Chloride
Dextran, High Molecular Weight
Dichloroacetic Acid
Diethylamine
Dimethyl Sulfoxide, Spectrophotometric Grade
2,4-Dinitrofluorobenzene
Disodium Chromotropate
1-Dodecanol
Eosin Y (Eosin Yellowish Y)
β-Galactosidase Suspension
Hexokinase and Glucose-6-phosphate Dehydrogenase Suspension
Hydriodic Acid
Hydrogen Sulfide Detector Tube
4-Hydroxybenzoic Acid Isopropyl Ester
Imidazole
Iron Wire
4-Isobutylacetophenone
Isoflupredone Acetate
Lactose
Lead Perchlorate
Lithium Chloride
Lithium Hydroxide
Lithium Perchlorate
Mercuric Nitrate
Mercuric Sulfate
Methoxyethanol
2-Methoxyethanol
p-Methylaminophenol Sulfate
N-Methylpyrrolidine
Monochloroacetic Acid
Monoethanolamine
2-Naphthyl Chloroformate
Nitric Oxide–Nitrogen Dioxide Detector Tube
Nitromethane
Olefin Detector Tube
Osmium Tetroxide
Periodic Acid
3-Phenoxybenzoic Acid
2-Phenylacetamide
Phenylglycine
Phthalic Acid
Potassium Dichromate
Potassium Phosphate, Monobasic
Potassium Phosphate, Tribasic
n-Propyl Alcohol
Reagent Footnotes
Sodium Acetate
Sodium Acetate, Anhydrous
Sodium Arsenite, Twentieth-Molar (0.05 M)
Sodium Borate
Sodium Bromide
Sodium Dichromate
Sodium 1-Decanesulfonate
Sodium Oxalate
Sodium Perchlorate
Sodium Pyrophosphate
Sodium Sulfate
Sodium Tetraphenylborate
Starch, Soluble, Purified
Succinic Acid
Sulfamic Acid
Sulfur Dioxide Detector Tube
Tannic Acid
Tetrabutylammonium Bromide
Tetrahydrofuran
Tetrahydrofuran, Stabilizer-Free
Tetramethylammonium Bromide
Thiourea
p-Toluenesulfonic Acid
Trichlorotrifluoroethane
Water Vapor Detector Tube
Zinc Acetate

(BPC: M. Marques) RTS—39837-2

Change to read:

Acetaldehyde, CH_3CHO—**44.05**—Colorless liquid. Miscible with water and alcohol.

~~*Assay*~~ ~~Inject an appropriate specimen into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a flame ionization detector, helium being used as the carrier gas. The following conditions have been found suitable: a 30-m × 0.25-mm capillary column coated with a 1-µm layer of phase G2; the injection port temperature is maintained at 30°; the detector temperature is maintained at 300°; the column temperature is maintained at 30° and programmed to rise 10° per minute to 150°. The area of the CH_3CHO peak is not less than 99% of the total peak area.~~

~~*Refractive index* ⟨831⟩: between 1.330 and 1.334, at 20°.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Acetyl Chloride, *USP 26* page 2462—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-3

Change to read:

Acetyl Chloride, CH_3COCl—**78.50**—Clear, colorless liquid, having a strong, pungent odor. Is decomposed by water and by alcohol. Miscible with benzene and with chloroform. Specific gravity: about 1.1.

~~*Boiling range* (Reagent test)~~ ~~Not less than 94% distils between 49° and 53°.~~

~~*Residue on evaporation*~~ ~~Evaporate 10 mL on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 2.5 mg (about 0.02%).~~

~~*Miscibility with benzene* and *with chloroform*~~ ~~Separate 5-mL portions give clear solutions with 20 mL of benzene and with 20 mL of chloroform.~~

~~*Solubility*~~ ~~Place 5 mL in a 50-mL graduated cylinder, and cautiously add, dropwise, about 3 mL of water, shaking after each addition until the reaction is complete, then dilute with water to 50 mL: the solution is clear.~~

~~*Phosphorus compounds*~~ ~~To 5 mL of the solution obtained in the preceding test add 3 mL of nitric acid, and evaporate on a steam bath to dryness. The residue, dissolved in 20 mL of water, shows not more than 0.03 mg of PO_4 (0.02% as P) [See *Phosphate in Reagents*].~~

~~*Heavy metals*~~ ~~Dilute 10 mL of the solution obtained in the test for *Solubility* with 30 mL of water, add 10 mL of hydrogen sulfide TS, and render alkaline with ammonia TS: no noticeable change in color is produced.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Albumin Bovine Serum. This new reagent is to be used in the *Total protein* test in the proposed monograph *Anthrax Vaccine Adsorbed*.

(HDQ: M. Marques) RTS—39997-1

Add the following:

■**Albumin Bovine Serum**— [*9048-46-8*]—Almost colorless to faintly yellow powder. Not less than 95% pure. Solubility, 40 mg in 1 mL of water. Molecular weight is approximately 66,000. Use a suitable grade. Store between 2° and 8°.■1S (*USP27*)

BRIEFING

Alum, *USP 26* page 2464—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-4

Change to read:

Alum (*Ammonium Alum*, *Aluminum Ammonium Sulfate*), $AlNH_4(SO_4)_2 \cdot 12H_2O$—**453.33**—Large, colorless crystals or crystalline fragments or a white powder. Soluble in 7 parts of water and in about 0.5 part of boiling water; insoluble in alcohol.

~~*Insoluble matter* (Reagent test): not more than 1 mg, from 10 g (0.01%).~~

~~*Chloride* (Reagent test)~~ ~~Two g shows not more than 0.02 mg of Cl (0.001%).~~

~~*Alkalies and alkaline earths*~~ ~~Dissolve 2 g in 140 mL of water, add 2 drops of methyl orange TS, then add ammonia TS in small portions until the color just turns yellow. Boil for 2 minutes, dilute with water to 150 mL, and filter. Evaporate 75 mL of the filtrate, and ignite the residue: the ignited residue weighs not more than 2.5 mg (0.25%).~~

~~*Arsenic* (Reagent test)~~ ~~The stain produced by 1 g does not exceed that produced by 0.002 mg of As (2 ppm as As).~~

~~*Heavy metals* (Reagent test): 0.001%.~~

~~*Iron* ⟨241⟩~~ ~~Dissolve 1.0 g in 40 mL of water, add 4 mL of hydrochloric acid, mix, and dilute with water to 50 mL. Dilute 25 mL of this solution with water to 47 mL: the solution shows not more than 0.01 mg of Fe (0.002%).~~

■Use ACS reagent grade.■1S (*USP27*)

In-Process Revision

BRIEFING

Alumina, Activated, *USP 26* page 2464—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-5

Change to read:

Alumina, Activated—Use a suitable grade.~~[2]~~

■■1S (*USP27*)

BRIEFING

4-Amino-3-hydroxy-1-naphthalenesulfonic Acid, *USP 26* page 2465—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-6

Change to read:

4-Amino-3-hydroxy-1-naphthalenesulfonic Acid, $C_{10}H_9NO_4S$—**239.25**—Light purple powder.
~~*Solubility in ammonium hydroxide*~~ ~~Dissolve 50 mg in 1 mL of ammonium hydroxide: the solution is dark brown.~~
~~*Melting point* ⟨741⟩: about 295°, with decomposition.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Ammonia Detector Tube, *USP 26* page 2465—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-7

Change to read:

Ammonia Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator bromophenol blue.

~~NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number CH 20501, Measuring Range 5 to 70 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.~~

■*Measuring range:* 5 to 70 ppm.[110]■1S (*USP27*)

BRIEFING

Ammonia Water, Stronger, *USP 26* page 2465—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-8

Change to read:

Ammonia Water, Stronger (*Ammonium Hydroxide*)—Use ACS reagent grade Ammonium Hydroxide.
~~*Assay* (as NH_3): 28.0% to 30%.~~

■■1S (USP27)

BRIEFING

Ammonium Hydroxide, 6 N. It is proposed to add this new reagent which is used to prepare a number of solutions used in the tests under *Heavy Metals* ⟨231⟩.

(HDQ: M. Marques) RTS—39889-1

Add the following:

■**Ammonium Hydroxide, 6 N**—Use Ammonia TS.■1S (*USP27*)

BRIEFING

Arsenic Trioxide, *USP 26* page 2468—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-9

Change to read:

Arsenic Trioxide, As_2O_3—**197.84**—Use ACS reagent grade. [NOTE—Arsenic Trioxide of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Office of Standard Reference Materials, ~~Washington, DC 20234,~~

■www.nist.gov,■1S (*USP27*)
as standard sample ~~No. 83b.~~

■No. 83.]■1S (*USP27*)

BRIEFING

Benzoic Acid, *USP 26* page 2469—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-10

Change to read:

Benzoic Acid, C_6H_5COOH—**122.12**—Use ACS reagent grade. [NOTE—Benzoic Acid of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Office of Standard Reference Materials, ~~Washington, DC 20234,~~

■www.nist.gov,■1S (*USP27*)
as standard sample No. 350.]

BRIEFING

7 Percent Bovine Serum Albumin Certified Standard, *USP 26* page 2471—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-9

Change to read:

7 Percent Bovine Serum Albumin Certified Standard—Available from the National Institute of Standards and Technology

■, www.nist.gov, as SRM 927.■1S (*USP27*)

BRIEFING

Butyl Acetate, Normal, *USP 26* page 2471—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-12

Change to read:

Butyl Acetate, Normal, $CH_3COO(CH_2)_3CH_3$—**116.16**~~—Clear, colorless liquid having a characteristic odor. Slightly soluble in water; miscible with alcohol. Specific gravity: about 0.88.~~

~~*Distilling range* ⟨721⟩—Not less than 95% distils between 123° and 126°.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Butyl Alcohol, *USP 26* page 2471—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-105

Change to read:

Butyl Alcohol (*1-Butanol; Normal Butyl Alcohol*), $CH_3(CH_2)_2CH_2OH$—**74.12**—Use ACS reagent grade. ~~1-Butanol.~~

■■1S (*USP27*)

BRIEFING

Butyl Alcohol, Tertiary, *USP 26* page 2471—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-13

Change to read:

Butyl Alcohol, Tertiary, $(CH_3)_3COH$—**74.12**~~—Colorless crystals, becoming liquid at a temperature above 25.5°. Has a camphoraceous odor. Miscible with water and with common organic solvents.~~

~~*Miscibility*—Mix a 5-mL portion with 15 mL of water, and mix another 5-mL portion with 15 mL of carbon disulfide. Allow each mixture to stand for 15 minutes: neither mixture is more turbid than an equal volume of the diluent.~~

~~*Specific gravity* ⟨841⟩: not less than 0.778 and not more than 0.782.~~

In-Process Revision

~~*Boiling range* (Reagent test): between 82.5° and 83.5°.~~
~~*Freezing point:* not less than 25°.~~
~~*Residue on evaporation*—Evaporate about 20 g, accurately weighed, in a crucible on a steam bath, and dry at 105° for 1 hour: not more than 0.005% is found.~~
~~*Acidity*—Add 20 mL of it to 20 mL of water previously neutralized to phenolphthalein TS with 0.02 *N* sodium hydroxide, mix, and titrate with 0.020 *N* sodium hydroxide until the pink color is restored: not more than 0.40 mL is required (about 0.003% as CH_3COOH).~~
~~*Alkalinity*—Dilute 10 mL with 20 mL of water, and add 1 drop of methyl red TS: if the solution is yellow, not more than 0.25 mL of 0.020 *N* sulfuric acid is required to change it to pink (about 0.001% as NH_3).~~

■—Use ACS reagent grade *tert*-butyl alcohol.■1S (*USP27*)

BRIEFING

***n*-Butylboronic Acid,** *USP 26* page 2472—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-15

Change to read:

***n*-Butylboronic Acid,** $C_4H_9B(OH)_2$—**101.94**—Use a suitable grade.~~11~~

■10
■1S (*USP27*)
[NOTE—This reagent is usually shipped and stored under water. Before use, remove any excess water by light vacuum filtration.]

BRIEFING

Calcium Acetate, *USP 26* page 2473—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-16

Change to read:

Calcium Acetate, $Ca(C_2H_3O_2)_2 \cdot H_2O$—**176.18**—White, crystalline granules or powder. Soluble in about 3 parts of water; slightly soluble in alcohol.
~~*Insoluble matter* (Reagent test): not more than 1.0 mg, from 10 g (0.010%).~~
~~*Alkalinity and acidity*—To a solution of 2.0 g in 25 mL of water add phenolphthalein TS: no pink color is produced. Then add 0.10 *N* sodium hydroxide until a pink color is produced after shaking: not more than 0.70 mL of the alkali is required (0.2% as CH_3COOH).~~
~~*Chloride* (Reagent test)—One g shows not more than 0.05 mg of Cl (0.005%).~~
~~*Sulfate* (Reagent test, *Method I*)—One g shows not more than 0.4 mg of SO_4 (0.04%).~~
~~*Alkalies and magnesium*—Dissolve 1 g in 50 mL of water. Add 2 mL of hydrochloric acid, heat to boiling, and add 35 mL of oxalic acid solution (1 in 20). Slowly neutralize the solution, while it is cooling, with stronger ammonia water, then dilute with water to 100 mL, and allow to stand for 4 hours or overnight. Filter, and to 50 mL of the filtrate add 5 drops of sulfuric acid, evaporate, and ignite to constant weight: not more than 1.5 mg of residue remains (0.3% as SO_4).~~
~~*Barium*—Dissolve 2 g in 15 mL of water, add 2 drops of glacial acetic acid, filter, and add to the filtrate 0.3 mL of potassium dichromate solution (1 in 10): no turbidity is produced within 10 minutes (about 0.01%).~~
~~*Heavy metals* (Reagent test): 0.001%.~~
~~*Iron* ⟨241⟩—Dissolve 500 mg in 47 mL of water containing 2 mL of hydrochloric acid. The solution shows not more than 0.01 mg of Fe (0.002%).~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Calcium Carbonate, *USP 26* page 2473—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-17

Change to read:

Calcium Carbonate, $CaCO_3$—**100.09**—Use ACS reagent grade.
NOTE—Calcium Carbonate of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Office of Standard Reference Materials, ~~Washington, DC 20234,~~

■www.nist.gov,■1S (*USP27*)
as standard sample No. 915.

BRIEFING

Calcium Chloride, Anhydrous, *USP 26* page 2473—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-18

Change to read:

Calcium Chloride, Anhydrous (for drying), $CaCl_2$—**110.98**—Use ACS reagent grade

■Calcium Chloride Desiccant.■1S (*USP27*)

BRIEFING

Carbon Dioxide Detector Tube, *USP 26* page 2474—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-19

Change to read:

Carbon Dioxide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it. Contains suitable absorbing filters and support media for the indicators hydrazine and crystal violet. ~~[NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number 81 01811, Measuring Range 0.01 to 0.3 Vol. %. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.]~~

■*Measuring range:* 0.01 to 0.3 Vol.–%.[110] ■1S (*USP27*)

BRIEFING

Carbon Monoxide Detector Tube, *USP 26* page 2474—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-20

Change to read:

Carbon Monoxide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it. Contains suitable absorbing filters and support media for the indicators iodine pentoxide and selenium dioxide and fuming sulfuric acid.

~~NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number CH 25601, Measuring Range 5 to 150 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.~~

■*Measuring range:* 5 to 150 ppm.[110] ■1S (*USP27*)

BRIEFING

Casein, *USP 26* page 2474—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-21

Change to read:

Casein~~[13]~~

■■1S (*USP27*)
—White or slightly yellow, odorless, granular powder. Insoluble in water and in other neutral solvents; readily dissolved by ammonia TS and by solutions of alkali hydroxides, usually forming a cloudy solution.

Residue on ignition (Reagent test)—Ignite 2 g: the residue weighs not more than 20 mg (1.0%).

Loss on drying ⟨731⟩—Dry it at 105° to constant weight: it loses not more than 10.0% of its weight.

Alkalinity—Shake 1 g with 20 mL of water for 10 minutes, and filter: the filtrate is not alkaline to red litmus paper.

Soluble substances—When the filtrate from the *Alkalinity* test is evaporated and dried at 105°, the residue weighs not more than 1 mg (0.1%).

Fats—Dissolve 1 g in a mixture of 10 mL of water and 5 mL of alcoholic ammonia TS, and shake out with two 20-mL portions of solvent hexane. Evaporate the hexane at a low temperature, and dry at 80°: the weight of the residue does not exceed 5 mg (0.5%).

Nitrogen content, *Method I* ⟨461⟩—Between 15.2% and 16.0% of N is found, on the anhydrous basis.

Where vitamin-free casein is required, use casein that has been rendered free from the fat-soluble vitamins by continuous extraction with hot alcohol for 48 hours followed by air-drying to remove the solvent.

BRIEFING

Cation-Exchange Resin, Styrene-Divinylbenzene, Strongly Acidic, *USP 26* page 2474—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-22

Change to read:

Cation-Exchange Resin, Styrene-Divinylbenzene, Strongly Acidic—Use a suitable grade.~~[17]~~

■[14] ■1S (*USP27*)

In-Process Revision

BRIEFING

Ceric Ammonium Sulfate, *USP 26* page 2474—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-23

Change to read:

Ceric Ammonium Sulfate, $Ce(SO_4)_2 \cdot 2(NH_4)_2SO_4 \cdot 2H_2O$—**632.55**—Yellow to yellowish orange crystals. Dissolves slowly in water, but more rapidly when mineral acids are present.

~~*Assay*—Weigh accurately about 1 g, dissolve in 10 mL of dilute sulfuric acid (1 in 10), and add 40 mL of water. Add orthophenanthroline TS, and titrate with freshly standardized 0.1 *N* ferrous ammonium sulfate VS. Each mL of 0.1 *N* ferrous ammonium sulfate is equivalent to 63.26 mg of $Ce(SO_4)_2 \cdot 2(NH_4)_2SO_4 \cdot 2H_2O$: not less than 94% is found.~~

~~*Iron*—Dissolve 100 mg in 30 mL of dilute sulfuric acid (1 in 10), and add hydrogen peroxide TS, dropwise, until the solution is colorless. Add stronger ammonia TS until the pH is between 1 and 3, cool to room temperature, further adjust to a pH of 3.5 (using a glass electrode), and dilute to 50 mL. To 5 mL of this solution add 5 mL of water, mix, and add 6 mL of hydroxylamine hydrochloride solution (1 in 10) and 4 mL of a slightly acidified solution of orthophenanthroline (1 in 1000): any red color produced is not darker than that of a control containing 0.1 mg of added Fe and the volumes of acid and hydrogen peroxide TS used with the test specimen (0.1%).~~

~~*Phosphate*—Dissolve 200 mg in 30 mL of dilute sulfuric acid (1 in 10), add 30 percent hydrogen peroxide until the solution is colorless, and boil to remove the excess peroxide. Cool, and dilute to 100 mL. To 5 mL of the resulting solution add 55 mL of water, and adjust to a pH of 2 to 3 with ammonium hydroxide. [NOTE—Adjust the pH carefully, since the formation of a permanent precipitate will interfere with succeeding operations. Should a permanent precipitate be formed, discard the solution, and start with a fresh aliquot of the test solution.]Add 500 mg of ammonium molybdate, and adjust to a pH of 1.8 (using a glass electrode) with dilute hydrochloric acid (1 in 10). Heat the solution to boiling, cool, add 10 mL of hydrochloric acid, and then dilute to 100 mL. Transfer to a separator, add 35 mL of ether, shake vigorously, allow to separate, and discard the water layer. Wash the ether layer twice by shaking with separate 10 mL portions of dilute hydrochloric acid (1 in 10), discarding the aqueous layer each time. Add 0.20 mL of a freshly prepared solution of 2 g of stannous chloride in 100 mL of hydrochloric acid, shake well, and allow the layers to separate: any blue color in the ether layer is not darker than that of a control prepared by adding the equivalent of 0.01 mg of PO_4 to 5 mL of dilute sulfuric acid (3 in 25) and treating exactly as the 5 mL of test solution (0.1%).~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Chloramine T, *USP 26* page 2475—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-24

Change to read:

Chloramine T (*Sodium p-Toluenesulfonchloramide*), $C_7H_7ClNNaO_2S \cdot 3H_2O$—**281.69**~~—White or faintly yellow efflorescent crystals or crystalline powder, having a slight odor of chlorine. Freely soluble in water and in boiling water; soluble in alcohol with decomposition; insoluble in benzene, in chloroform, and in ether. Store in tight containers, protected from light, in a cold place.~~

~~*Assay*—Weigh accurately about 400 mg, and dissolve in 50 mL of water. Add, in the order named, 10 mL of potassium iodide TS and 5 mL of diluted sulfuric acid, allow to stand for 10 minutes, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate VS. Each mL of 0.1 *N* sodium thiosulfate solution is equivalent to 14.1 mg of $C_7H_7ClNNaO_2S \cdot 3H_2O$. Between 98.0% and 103.0% of $C_7H_7ClNNaO_2S \cdot 3H_2O$ is found.~~

~~*Ortho compound*—Boil 2.0 g with a mixture of 10 mL of water and 1.0 g of sodium metabisulfite, cool in ice, and filter rapidly: the residue, after being washed with three 5-mL portions of ice-cold water and dried in vacuum over phosphorus pentoxide, melts at a temperature not lower than 134°.~~

~~*Sodium chloride*—Weigh accurately about 1 g, shake with 15 mL of dehydrated alcohol, filter, wash the residue with two 5-mL portions of dehydrated alcohol, and dry at 105° to constant weight: the residue represents not more than 1.5% of the weight taken.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Chlorine Detector Tube, *USP 26* page 2475—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-25

Change to read:

Chlorine Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator *o*-tolidine. ~~[NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number CH 24301,Measuring Range 0.2 to 3 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.]~~

■*Measuring range:* 0.2 to 3 ppm.[110]■1S (*USP27*)

BRIEFING

***p*-Chloroaniline,** *USP 26* page 2476—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-26

Change to read:

***p*-Chloroaniline,**

■(*4-Chloroaniline*),■1S (*USP27*)
C_6H_6ClN—**127.57** [*106-47-8*]—Use a suitable grade.~~21~~

■■1S (*USP27*)

BRIEFING

Chlorobenzene, *USP 26* page 2476—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-27

Change to read:

Chlorobenzene, C_6H_5Cl—**112.56**—Clear, colorless liquid having a characteristic odor. Insoluble in water; soluble in alcohol, in benzene, in chloroform, and in ether.

~~*Specific gravity* ⟨841⟩: between 1.100 and 1.111.~~

~~*Boiling range* (Reagent test): not less than 95% distils between 129° and 131°.~~

~~*Acidity*—To 200 mL of methanol add methyl red TS, and neutralize with 0.1 *N* sodium hydroxide, disregarding the amount of alkali consumed. Dissolve 23 mL of the test specimen in the neutralized methanol, and titrate with 0.10 *N* sodium hydroxide: not more than 1.0 mL is required to neutralize the specimen (about 0.015% as HCl).~~

~~*Residue on evaporation*—Evaporate 91 mL on a hot plate, and dry at 105° for 30 minutes: the residue weighs not more than 10 mg (about 0.010%).~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Chloroform, Alcohol-free, *USP 26* page 2476—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-28

Change to read:

Chloroform, Alcohol-free—Use a suitable grade~~,~~~~22~~

■which does not contain alcohol as a stabilizer.■1S (*USP27*)

BRIEFING

4-Chloro-1-Naphthol. This new reagent is to be used in the *Identification* test in the proposed monograph *Anthrax Vaccine Adsorbed*.

(HDQ: M. Marques) RTS—39998-3

Add the following:

■**4-Chloro-1-Naphthol,** $C_{10}H_7ClO$—**178.6** [*604-44-4*]—A white to off-white powder, with a melting point between 118° and 120°. Use a suitable grade. Store below 0°.■1S (*USP27*)

BRIEFING

Chromatographic Reagents, *USP 26* page 2477—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-29

Change to read:

Chromatographic Reagents—

■See *Chromatography* ⟨621⟩.■1S (*USP27*)
[NOTE—Listings of the numerical designations for phases (G), packings (L), and supports (S), together with corresponding brand names, are published periodically in *Pharmacopeial Forum* as a guide for the chromatographer.]

In-Process Revision

BRIEFING

Chromotropic Acid, *USP 26* page 2477—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-30

Change to read:

Chromotropic Acid (*4,5-Dihydroxy-2,7-naphthalenedisulfonic Acid*), $C_{10}H_8O_8S_2 \cdot 2H_2O$—**356.33**—Use ~~ACS reagent grade.~~

■a suitable grade.■1S (*USP27*)

BRIEFING

Cobaltous Acetate, *USP 26* page 2477—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-31

Change to read:

Cobaltous Acetate (*Cobalt Acetate*), $Co(C_2H_3O_2)_2 \cdot 4H_2O$—**249.08**—Red, needle-like crystals. Soluble in water and in alcohol.

~~*Insoluble matter* (Reagent test): not more than 1 mg, from 5 g, dissolved in 100 mL of water containing 2 mL of glacial acetic acid (0.02%).~~

~~*Chloride* (Reagent test)—One g shows not more than 0.1 mg of Cl (0.01%).~~

~~*Nitrate*—Dissolve 500 mg in 10 mL of water, add, with stirring, 10 mL of sodium hydroxide TS, and heat on a steam bath for 30 minutes. Cool, dilute with water to 20 mL, mix, and filter. To 10 mL of the filtrate add 5 mg of sodium chloride, 0.1 mL of indigo carmine TS, and 10 mL of sulfuric acid: the blue color does not entirely disappear in 1 minute (about 0.02%).~~

~~*Sulfate* (Reagent test, *Method II*)—The filtrate from the test for *Insoluble matter*, exclusive of washings, yields not more than 2.5 mg of residue (0.02%).~~

~~*Substances not precipitated by hydrogen sulfide*—Dissolve 2 g in about 90 mL of water, and add 2 g of ammonium chloride and sufficient ammonia TS to redissolve the precipitate first formed. Pass hydrogen sulfide into this solution until the cobalt is completely precipitated. Dilute with water to 100.0 mL, mix, and filter. Evaporate 50 mL of the filtrate nearly to dryness, add 0.5 mL of sulfuric acid, and ignite at 800 ± 25° to constant weight: the residue weighs not more than 3 mg (0.3% as SO_4).~~

~~*Copper*—Dissolve 500 mg in 30 mL of water, and add 1 mL of hydrochloric acid (A). Dissolve another 500 mg in 20 mL of water, and add 1 mL of hydrochloric acid and 10 mL of hydrogen sulfide TS (B). No difference in color between A and B is noticeable.~~

~~*Nickel*—Dissolve 1 g in 200 mL of water, add 1 g of sodium citrate, heat to boiling, add 100 mL of an alcohol solution of dimethylglyoxime (1 in 100), then add 15 mL of ammonia TS, and allow to stand overnight. Filter through a tared filtering crucible, wash with water, then with diluted alcohol, and dry at 105° to constant weight: the precipitate weighs not more than 25 mg (0.5%).~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Compactin, *USP 26* page 2478—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-32

Change to read:

Compactin, $C_{23}H_{34}O_5$—**390.52** [*73573-88-3*]—Use a suitable grade.~~s~~

■[10]■1S (*USP27*)

BRIEFING

Coomassie Blue G-250. This new reagent is to be used in the *Identification*, *Western Blot* and *Total protein content* tests in the proposed monograph *Anthrax Vaccine Adsorbed*.

(HDQ: M. Marques) RTS—39997-2

Add the following:

■**Coomassie Blue G-250** (*Coomassie Brilliant Blue G-250*, *Serva Blue G*), $C_{47}H_{48}N_3O_7S_2Na$—**854.0** [*6104-58-1*]—A dark blue powder. Soluble in water. Use a suitable grade. Store between 15° and 30°.■1S (*USP27*)

BRIEFING

Cupric Chloride, *USP 26* page 2478—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-33

Change to read:

Cupric Chloride, $CuCl_2 \cdot 2H_2O$—**170.48**—Bluish green deliquescent crystals. Freely soluble in water; soluble in alcohol; slightly soluble in ether.

~~*Insoluble matter* (Reagent test): not more than 1.0 mg, from 10 g (0.010%). Save the combined filtrate and washings for the test for *Sulfate*.~~

~~*Nitrate*—Dissolve 500 mg in 30 mL of dilute sulfuric acid (1 in 30). Slowly add the solution, with constant stirring, to 20 mL of sodium hydroxide solution (1 in 10), and digest on a steam bath for 15 minutes. Cool, with water dilute to 50 mL, and filter. To 10 mL of the clear filtrate, add 0.05 mL of indigo carmine TS followed by 10 mL of sulfuric acid: the blue color does not entirely disappear within 5 minutes (about 0.15%).~~

~~*Sulfate* (Reagent test, *Method II*)—The combined filtrate and washings retained from the test for *Insoluble matter* yield not more than 1.2 mg of residue (0.005%).~~

~~*Substances not precipitated by hydrogen sulfide*—Dissolve 2 g in 100 mL of water, add 1 mL of sulfuric acid, heat the solution to 70°, and pass hydrogen sulfide into the solution until the copper is completely precipitated. Allow the precipitate to settle, and filter without washing. Transfer 50.0 mL of the filtrate to a tared evaporating dish, and evaporate on a steam bath to dryness. Gently ignite the dish over a flame, and then at 800 ± 25° to constant weight. Cool, and weigh: the residue weighs not more than 1.0 mg (0.1%). Retain the residue for the *Iron* test.~~

~~*Iron* ⟨241⟩—To the residue retained from the preceding test, add 2 mL of hydrochloric acid, 2 mL of water, and 0.05 mL of nitric acid. Evaporate slowly on a steam bath to dryness, then take up the residue in 1 mL of hydrochloric acid and 10 mL of water. Dilute with water to 100 mL, and mix. To 20 mL of the dilution add 10 mL of water, and mix: 10 mL of this solution shows not more than 0.01 mg of Fe (0.015%). Retain the residue dilution for use in the test for *Other metals*.~~

~~*Other metals*—To 20 mL of the residue solution retained from the test for *Iron* add a slight excess of ammonium hydroxide, boil the solution for 1 minute, filter, and wash the residue with water until the combined filtrate and washings measure 20 mL. Neutralize the filtrate with diluted hydrochloric acid, dilute with water to 25 mL, and add 0.15 mL of ammonium hydroxide and 1 mL of hydrogen sulfide TS: any color produced is not darker than that of a control containing, in the same volume, 0.15 mL of ammonium hydroxide, 1 mL of hydrogen sulfide TS, and 0.02 mg of added Ni (0.01% as Ni).~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Dextran, High Molecular Weight, *USP 26* page 2479—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-34

Change to read:

Dextran, High Molecular Weight—A dextran molecular weight standard having a weight-average molecular weight, M_W, of 1 to 2×10^6 Da and a weight-average molecular weight to number-average molecular weight ratio, M_W/M_N, of 1.0 to 1.8.~~93~~

■10■1S (*USP27*)

BRIEFING

Dichloroacetic Acid. This new reagent is used in the test for *Limit of sodium chloride and sodium sulfate* under *Sodium Cetostearyl Sulfate*, which appears elsewhere in this number of *PF*.

(HDQ: E. Gonikberg; M. Marques) RTS—39843-2

Add the following:

■**Dichloroacetic Acid,** $C_2H_2Cl_2O_2$—**128.9** [*79-43-6*]—Colorless liquid. Miscible with water, with alcohol, and with ether. Use a suitable grade.■1S (*USP27*)

BRIEFING

Diethylamine, *USP 26* page 2481—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-35

Change to read:

Diethylamine, $(C_2H_5)_2NH$—**73.14**—Colorless, flammable, strongly alkaline liquid. Miscible with water and with alcohol. Forms a hydrate with water. *May be irritating to skin and mucous membranes*. Store in well-closed containers.

~~*Assay*—To 50 mL of water add 6 to 8 drops of a freshly prepared mixed indicator (prepared by mixing 5 parts of a 1 in 1000 solution of bromocresol green in methanol with 1 part of a 1 in 1000 solution of methyl red in methanol), and neutralize with 0.1 *N* hydrochloric acid to the disappearance of the green color. Weigh accurately about 2 g of specimen in a tared, glass-stoppered, 250 mL conical flask containing a few mL of the neutralized water. Add the remainder of the neutralized water, and titrate with 1 *N*~~

~~hydrochloric acid VS to the disappearance of the green color. Each mL of 1 *N* hydrochloric acid is equivalent to 73.1 mg of $(C_2H_5)_2NH$. Not less than 99.0% is found.~~

~~*Specific gravity* ⟨841⟩: between 0.700 and 0.705.~~

~~*Boiling range* (Reagent test): between 55° and 58°.~~

~~*Residue after evaporation*—Evaporate 14 mL (10 g) in a tared dish on a steam bath to dryness, dry at 105° for 1 hour, cool, and weigh: the weight of the residue does not exceed 1.0 mg (0.010%).~~

~~*Water-insoluble substances*—Transfer 25 mL to a 125-mL conical flask, and add 25 mL of water in 5-mL portions, shaking the flask well after each addition. Add another 25 mL of specimen to 25 mL of water in the same manner. No cloudiness or turbidity is produced in either instance.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

1,3-Dimethyl-2-imidazolidinone. This new reagent is used as a component of the *Test solution for dimethylformamide and N,N-dimethyl acetamide* in *Procedure A for Water-Insoluble Articles* in the section *Identification, Control, and Quantification of Residual Solvents* under *Organic Volatile Impurities* ⟨467⟩, which appears in the *In-Process Revision* section of this *PF*.

(HDQ: M. Marques) RTS—39967-3

Add the following:

■**1,3-Dimethyl-2-imidazolidinone,** $C_5H_{10}N_2O$—**114.15**

[*80-73-9*]—Use a suitable grade.■1S (*USP27*)

BRIEFING

Dimethyl Sulfoxide, Spectrophotometric Grade, *USP 26* page 2482—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-36

Change to read:

Dimethyl Sulfoxide, Spectrophotometric Grade—Use methyl sulfoxide ~~reagent meeting the following additional specifications:~~

~~*Assay*—Inject an appropriate specimen (about 0.1 µL) into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal conductivity detector, and obtain the chromatogram. Under typical conditions, the instrument contains a 2-m × 3-mm glass column packed with 20% phase G16 on support S1. The column is maintained at about 95°, and the injection port and the thermal conductivity detector block are maintained at about 180°. Helium is used as the carrier gas at a flow rate of about 50 mL per minute. The area of the symmetric methyl sulfoxide peak is at least 99% of the total peak area.~~

~~*Ultraviolet absorption*—Determine the UV absorbance of the specimen in a 1-cm cell, from 400 to 262 nm, using water as the blank: the absorbance does not exceed 1.00 at 262 nm, 0.360 at 270 nm, 0.080 at 300 nm, and 0.010 in the range of 340 to 400 nm. The absorbance curve is smooth and does not show extraneous absorbances within the range observed.~~

■ACS reagent grade.■1S (*USP27*)

BRIEFING

2,4-Dinitrofluorobenzene, *USP 26* page 2484—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-37

Change to read:

2,4-Dinitrofluorobenzene (*1-Fluoro-2,4-dinitrobenzene*), $C_6H_3FN_2O_4$—**186.10**—Light yellow solid.

~~*Assay*—Inject an appropriate specimen (about 0.2 µL) into a suitable gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: a 1.8-m × 4-mm stainless steel column containing 10% phase G1 on support S1A; the injection port and detector are maintained at 290° and 300°, respectively; the column temperature is maintained at 140° and programmed to rise 3° per minute to 190°. The area of the 2,4-dinitrofluorobenzene peak is not less than 99% of the total peak area.~~

~~*Melting range* ⟨741⟩: between 28° and 31°.~~

■Use a suitable grade.■1S (*USP27*)

BRIEFING

Disodium Chromotropate, *USP 26* page 2484—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-38

Change to read:

Disodium Chromotropate (*4,5-Dihydroxy-2,7-naphthalenedisulfonic Acid, Disodium Salt*), $C_{10}H_6O_8S_2Na_2 \cdot 2H_2O$—**400.29**—Use ACS reagent grade

■Chromotropic Acid Disodium Salt.■1S (*USP27*)

BRIEFING

1-Dodecanol, *USP 26* page 2484—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-39

Change to read:

1-Dodecanol (*Dodecyl Alcohol*), $CH_3(CH_2)_{11}OH$—**186.33**—A clear, colorless liquid. Crystallizes as leaflets from dilute alcohol solution.

~~*Melting range* ⟨741⟩: between 23° and 25°.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Dodecyl Lithium Sulfate. This new reagent is to be used in the *Identification* test in the proposed monograph *Anthrax Vaccine Adsorbed*.

(HDQ: M. Marques) RTS—39998-1

Add the following:

■**Dodecyl Lithium Sulfate** (*Lithium Dodecyl Sulfate*, *Lithium Lauryl Sulfate*), $C_{12}H_{25}LiO_4S$—**272.3** [*2044-56-6*]—White to off-white powder, clear to slightly hazy, colorless to faint yellow solution in water at 50 mg per mL at ambient temperature. The UV absorbance of a 0.1 M solution is less than 0.05 at both 260 and 280 nm. The pH of a 0.1 M solution in water is 7.0 ± 0.5. Use a suitable grade.■1S (*USP27*)

BRIEFING

Eosin Y (Eosin Yellowish Y), *USP 26* page 2484—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-40

Change to read:

Eosin Y (Eosin Yellowish Y) (*Certified Biological Eosin Y; Sodium Tetrabromofluorescein*), $C_{20}H_6Br_4Na_2O_5$—**691.85**—Red to brownish red pieces or powder. ~~One g dissolves in about 2 mL of water and in 50 mL of alcohol.~~

~~*Color characteristics*—Its 1 in 500 solution is yellowish to purplish red with a greenish fluorescence. Its 1 in 12,000 alcohol solution is pink to purplish red with a greenish yellow fluorescence. The addition of mineral acids to a solution (1 in 100) produces an orange to reddish orange precipitate of tetrabromofluorescein. On the addition of 2 mL of saturated sodium hydroxide solution to 10 mL of a solution of the dye (1 in 100), a red precipitate is formed.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

β**-Galactosidase Suspension,** *USP 26* page 2488—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-41

Delete the following:

~~■**β-Galactosidase Suspension**—Use a suitable grade.[33]~~

~~*Suitability*—When used to assay lactulose, determine that a suitable absorbance versus concentration slope is obtained using USP Lactulose RS, the reagent blank absorbance being not more than 0.020.~~■1S (*USP27*)

BRIEFING

1-Heptadecanol. This new reagent is used to prepare the *Internal standard solution* in the *Assay* under *Sodium Cetostearyl Sulfate*, which appears elsewhere in this number of *PF*.

(HDQ: M. Marques) RTS—39843-3

Add the following:

■**1-Heptadecanol**, $C_{17}H_{36}O$—**256.48** [*1454-85-9*]—Use a suitable grade.■1S (*USP27*)

In-Process Revision

BRIEFING

Hexokinase and Glucose-6-phosphate Dehydrogenase Suspension, *USP 26* page 2489—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-44

Delete the following:

■~~**Hexokinase and Glucose-6-phosphate Dehydrogenase Suspension**—Use a suitable grade.[22]~~

~~*Suitability*—When used in the assay of lactulose, determine that a suitable absorbance-versus-concentration slope is obtained, using USP Lactulose RS, the reagent blank absorbance being not more than 0.020.~~■1S (*USP27*)

BRIEFING

Horseradish Peroxidase Conjugated to Goat Anti-Mouse IgG. This new reagent is to be used in the *Identification* test in the proposed monograph *Anthrax Vaccine Adsorbed*.

(HDQ: M. Marques) RTS—39998-4

Add the following:

■**Horseradish Peroxidase Conjugated to Goat Anti-Mouse IgG**—Affinity purified polyclonal antibody to Mouse Immune globulin (IgG) heavy and light chains (whole IgG) produced in Goat and labeled with horseradish peroxidase. Available either as a lyophilized powder or as a solution in a suitable buffer, generally 10 mM sodium phosphate, pH 7.4, containing a suitable preservative, such as 0.01% thimerosal, and an inactive protein(s) to prevent adsorption on the surface of the container. Use a suitable grade. Store at –20°.■1S (*USP27*)

BRIEFING

Hydriodic Acid, *USP 26* page 2489—See briefing under Acetaldehyde.

(HDQ: M. Marques) RTS—39837-42

Change to read:

Hydriodic Acid, HI—**127.91**—Use ACS reagent grade (containing not less than 47.0% of HI).

NOTE—For methoxy determination (see *Methoxy Determination* ⟨431⟩), use hydriodic acid ~~that is labeled "for alkoxyl determination," or that is purified as directed under *Methoxy Determination* ⟨431⟩.~~

■ACS reagent grade 55%.■1S (*USP27*)
Use this grade also for alkoxyl determinations in assays in the individual monographs.

BRIEFING

Hydrogen Sulfide Detector Tube, *USP 26* page 2489—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-43

Change to read:

Hydrogen Sulfide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator, the latter consisting of a suitable lead salt.

~~NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number 8101831, Measuring Range 1 to 20 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.~~

■*Measuring range:* 1 to 20 ppm.[110]■1S (*USP27*)

BRIEFING

4-Hydroxybenzoic Acid Isopropyl Ester, *USP 26* page 2490—See briefingunder *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-45

Change to read:

4-Hydroxybenzoic Acid Isopropyl Ester, $HOC_6H_4COOCH(CH_3)_2$—**180.18**—Use a suitable grade.[36]

■[8] ■1S (*USP27*)
Melting range ⟨741⟩: between 84° and 87°.

BRIEFING

Imidazole, *USP 26* page 2490—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-46

Change to read:

Imidazole, $C_3H_4N_2$—**68.08**—White to light yellow crystals. Freely soluble in water.

~~*Assay*—Transfer about 0.7 g, accurately weighed, to a 250-mL beaker. Dissolve in 100 mL of glacial acetic acid. Titrate with 0.1 *N* perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* perchloric acid is equivalent to 6.808 mg of $C_3H_4N_2$. Not less than 98% is found.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Iron Wire, *USP 26* page 2491—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-47

Change to read:

Iron Wire, Fe—**At. Wt. 55.847**—Use ~~ACS reagent grade.~~

■a suitable grade.■1S (*USP27*)

BRIEFING

4-Isobutylacetophenone, *USP 26* page 2491—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-48

Change to read:

4-Isobutylacetophenone, $C_{12}H_{16}O$—**176**—Pale yellow liquid. Soluble in chloroform, in glycerols, in alcohols, in ether, and in fatty oils; insoluble in water. Use a suitable grade.[38]

■[8] ■1S (*USP27*)

BRIEFING

Isoflupredone Acetate, *USP 26* page 2491—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-49

Change to read:

Isoflupredone Acetate[39]

■ ■1S (*USP27*)
(*9-α-Fluoroprednisolone Acetate*), $C_{23}H_{29}FO_6$—**420.47**—~~White to yellowish white powder. Insoluble in water; freely soluble in pyridine; soluble in alcohol and in dioxane; slightly soluble in chloroform. Melts at about 240°, with decomposition.~~

~~*Loss on drying* ⟨731⟩—Dry it at 105° for 4 hours: it loses not more than 1.0% of its weight.~~

■—Use Isoflupredone Acetate USP.■1S (*USP27*)

BRIEFING

Lactose, *USP 26* page 2491—See briefng under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-50

Change to read:

Lactose, ~~$C_{12}H_{22}O_{11}$~~

■$C_{12}H_{22}O_{11} \cdot H_2O$■1S (*USP27*)
—**342.30**—Use ACS reagent grade.

In-Process Revision

BRIEFING

Lead Perchlorate, *USP 26* page 2492—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-51

Change to read:

Lead Perchlorate, $Pb(ClO_4)_2 \cdot 3H_2O$—**460.15**—~~White crystals.~~

~~*Assay*—Transfer about 1.8 g, accurately weighed, to a suitable container, and dissolve in 50 mL of water. Pass the solution through a suitable short cation-exchange column, collecting the eluate in a suitable container. Wash the column with water until the eluate is neutral to blue litmus, and combine the washings with the first eluate. Add 5 drops of phenolphthalein TS, and titrate with 0.1 N sodium hydroxide VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N sodium hydroxide is equivalent to 23.01 mg of $Pb(ClO_4)_2 \cdot 3H_2O$.~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Lithium Chloride, *USP 26* page 2492—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-52

Change to read:

Lithium Chloride, LiCl—**42.39**—~~White, deliquescent crystals or granules. Freely soluble in water; soluble in acetone, in alcohol, in amyl alcohol, and in ether. Preserve in tight containers.~~

~~*Assay*—Dissolve about 1.3 g, previously dried at 120° for 1 hour and accurately weighed, in water to make 50.0 mL. Pipet 5 mL of the solution into a 250-mL conical flask, and add 5 mL of glacial acetic acid, 50 mL of methanol, and 2 drops of eosin Y TS. Titrate slowly with 0.1 *N* silver nitrate VS, adding it dropwise toward the end, until the color changes to an intense, slightly fluorescent red. Each mL of 0.1 *N* silver nitrate is equivalent to 4.239 mg of LiCl. Not less than 98% is found.~~

~~*Neutrality*—Dissolve 2 g in 20 mL of water, and add 1 drop of methyl red TS: any red color produced is changed to yellow on the addition of not more than 0.30 mL of 0.020 *N* sodium hydroxide. Any yellow color produced is changed to pink on the addition of not more than 0.30 mL of 0.020 *N* hydrochloric acid.~~

~~*Insoluble matter* (Reagent test): not more than 1.0 mg, from 10 g (0.010%).~~

~~*Nitrate* (Reagent test)—A 1-g portion dissolved in 2 mL of water shows no more color than that observed in 1.0 mL of *Standard Nitrate Solution* (0.001%).~~

~~*Phosphate* (Reagent test)—A 2-g portion shows not more than 0.02 mg of PO_4 (0.001%).~~

~~*Sulfate* (Reagent test, *Method I*)—A 1-g portion shows not more than 0.2 mg of SO_4 (0.02%).~~

~~*Ammonium*—~~

~~STANDARD AMMONIUM SOLUTION—Dissolve 296 mg of ammonium chloride in water to make 1 liter. This solution contains the equivalent of 0.1 mg of ammonium (NH_4) per mL.~~

~~PROCEDURE—To a solution of 900 mg in 50 mL of water add 1 mL of sodium hydroxide solution (1 in 10) and 2 mL of alkaline mercuric-potassium iodide TS: no more color is produced than that produced by 0.3 mL of *Standard Ammonium Solution*, diluted with water to 50 mL and treated similarly (0.003%).~~

~~*Barium*—Dissolve 2 g in 20 mL of water, filter, and divide the filtrate into two equal portions. To one portion add 1 mL of diluted sulfuric acid, and to the other add 1 mL of water: after 2 hours, the two portions are equally clear.~~

~~*Calcium* (Reagent test)—Dissolve 2.50 g in water to make 100 mL (*Test Solution*). Dissolve another 2.50 g in a mixture of 5.00 mL of *Standard Calcium Solution* and water to make 100 mL (*Control Solution*). Determine the calcium as directed under *Flame Photometry for Reagents* (Reagent test) (0.02%).~~

~~*Heavy metals* (Reagent test): 0.001%.~~

~~*Iron* ⟨241⟩—A solution of 500 mg in 47 mL of water containing 2 mL of hydrochloric acid shows not more than 0.01 mg of Fe (0.002%).~~

~~*Magnesium*—~~

~~STANDARD MAGNESIUM SOLUTION—Dissolve 1.014 g of clear, non-efflorescent crystals of magnesium sulfate in water to make 1 liter. This solution contains the equivalent of 0.1 mg of magnesium (Mg) per mL.~~

~~PROCEDURE—To a solution of 1 g in 45 mL of water add 0.5 mL of thiazole yellow solution (1 in 10,000) and 5 mL of sodium hydroxide solution (1 in 10): no more pink color is produced than that produced by 1 mL of *Standard Magnesium Solution*, diluted with water to 45 mL and treated similarly (0.1%).~~

~~*Potassium* (Reagent test)—Dissolve 5.0 g in water to make 100 mL (*Sample Solution*). Dissolve another 5.0 g in a mixture of 1.00 mL of *Standard Potassium Solution* and water to make 100 mL (*Control Solution*). Determine the potassium as directed under *Flame Photometry for Reagents* (Reagent test) (0.01%).~~

~~*Sodium* (Reagent test)—Dissolve 0.20 g in water to make 100 mL (*Test Solution*). Dissolve another 0.20 g in a mixture of 20 mL of *Standard Sodium Solution* and water to make 100 mL (*Control Solution*). Determine the sodium as directed under *Flame Photometry for Reagents* (Reagent test) (0.1%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Lithium Hydroxide, *USP 26* page 2492—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-53

Change to read:

Lithium Hydroxide, $LiOH \cdot H_2O$—**41.96**—~~White crystals. Soluble in water; insoluble in alcohol.~~

~~*Assay*—Dissolve about 160 mg, accurately weighed, in 50 mL of water, add phenolphthalein TS, and titrate with 0.1 *N* hydrochloric acid VS to a colorless end point. Each mL of 0.1 *N* hydrochloric acid is equivalent to 4.196 mg of $LiOH \cdot H_2O$. Not less than 98% is found.~~

~~*Insoluble matter* (Reagent test): not more than 1.0 mg, from 10 g (0.01%).~~

~~*Chloride* (Reagent test)—A 200-mg portion shows not more than 0.02 mg of Cl (0.01%).~~

~~*Sulfate* (Reagent test, *Method I*)—Dissolve 400 mg in 10 mL of water, and neutralize with *3 N* hydrochloric acid. Add 0.1 mL of bromine TS, boil to remove the excess bromine, add 2 mL of *3 N* hydrochloric acid, filter, and dilute with water to 40 mL: 20 mL of this solution shows not more than 0.10 mg of SO_4 (0.05%).~~

~~*Heavy metals* (Reagent test): 0.002%.~~

~~*Iron* ⟨241⟩: One g shows not more than 0.02 mg of Fe (0.002%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Lithium Perchlorate, *USP 26* page 2493—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-54

Change to read:

Lithium Perchlorate, $LiClO_4$—**106.39**~~—Small, white crystals. Freely soluble in water; sparingly soluble in alcohol, in acetone, in ether, and in ethyl acetate.~~

~~*Insoluble matter* (Reagent test): not more than 1 mg, from 20 g, dissolved in 200 mL of water (0.005%).~~

~~*pH:* between 6.0 and 7.5, in a solution of 10 g in 200 mL of ammonia- and carbon dioxide-free water.~~

~~*Chloride* (Reagent test)—One g shows not more than 0.03 mg of Cl (0.003%).~~

~~*Sulfate* (Reagent test, *Method II*)—Dissolve 40 g in 300 mL of water, add 2 mL of hydrochloric acid, and heat the solution to boiling. Add 5 mL of barium chloride TS, digest on a steam bath for 2 hours, and allow to stand overnight. If any precipitate is formed, filter, wash thoroughly, and ignite: the residue weighs not more than 1 mg (0.001%).~~

~~*Heavy metals* (Reagent test): 5 ppm.~~

~~*Iron*—Dissolve 1 g in water, and dilute with water to 20 mL. Add 1 mL of hydroxylamine hydrochloride solution (1 in 10), 4 mL of a slightly acidified solution of orthophenanthroline, and 1 mL of sodium acetate solution (1 in 10), and allow to stand for 1 hour: any red color produced is not darker than that of a control containing 0.005 mg of added Fe (5 ppm).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Mercuric Nitrate, *USP 26* page 2493—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-55

Change to read:

Mercuric Nitrate, ~~$Hg(NO_3)_2 \cdot H_2O$~~

■$Hg(NO_3)_2 \cdot xH_2O$■1S (*USP27*)
—**342.62**—Use ACS reagent grade.

■This reagent is available as either the mono- or dihydrate.■1S (*USP27*)

BRIEFING

Mercuric Sulfate, *USP 26* page 2478—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-57

Change to read:

Mercuric Sulfate, $HgSO_4$—**296.65**~~—Fine, white, heavy powder. Is odorless. One g dissolves in about 20 mL of sodium chloride solution (1 in 5)~~

~~*Assay*—Weigh accurately about 500 mg, and dissolve in 50 mL of dilute nitric acid (1 in 2). Add 1 mL of ferric nitrate solution (1 in 10), and titrate with 0.1 *N* ammonium thiocyanate VS. Each mL of 0.1 *N* ammonium thiocyanate consumed is equivalent to 10.03 mg of Hg. Between 67% and 67.5% of Hg is found.~~

~~*Residue on ignition*—Ignite 10 g at a rate such that 1 to 2 hours is required to volatilize the test specimen, and ignite at 800 ± 25° for 15 minutes: the residue weighs not more than 1 mg (0.01%).~~

~~*Chloride*—Mix 1 g with 50 mL of water, add 1 mL of formic acid, and add, dropwise, sodium hydroxidesolution (1 in 10) until a small amount of permanent precipitate is formed. Reflux the suspension until all of the mercury is reduced to metal and the solution is clear. Cool, filter through a chloride-free paper, wash with two 15-mL portions of water, and dilute with water to 90 mL. To 30 mL add 1 mL of nitric acid and 1 mL of silver nitrate TS, mix, and allow to stand for 5 minutes: any turbidity produced does not exceed that of a control prepared by adding 0.01 mg of Cl to 30 mL of water and treating as the 30 mL of test solution (0.003%).~~

In-Process Revision

~~*Iron* ⟨241⟩—To the *Residue on ignition* add 3 mL of dilute hydrochloric acid (1 in 2), cover with a watch glass, and digest on a steam bath for 20 minutes. Remove the watch glass, and evaporate to dryness. Take up the residue in a mixture of 1 mL of dilute hydrochloric acid (1 in 2) and 30 mL of water, filter if necessary, and dilute with water to 100 mL. To 10 mL of the solution add 2 mL of hydrochloric acid, and dilute with water to 47 mL: the solution shows not more than 0.01 mg of Fe (0.001%).~~

~~*Mercurous mercury*—Place 5.0 g in a glass-stoppered flask, add 100 mL of potassium iodide solution (15 in 100), 5.0 mL of 0.1 *N* iodine VS, and 3 mL of 1 *N* hydrochloric acid, and allow to stand in the dark, with frequent agitation, for 1 hour. Titrate the excess iodine with 0.1 *N* sodium thiosulfate VS, adding 3 mL of starch TS as the endpoint is approached: not more than 0.38 mL of the 0.1 *N* iodine is consumed, correction being made for any iodine consumed in a blank (0.15%).~~

~~*Nitrate*—Disperse 1 g in 9 mL of water, add 1 mL of sodium chloride solution (1 in 200), mix, and add 0.1 mL of indigo carmine TS and 10 mL of sulfuric acid: the blue color of the clear solution is not entirely discharged within 5 minutes (0.005%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Methenamine. This new reagent is used to prepare *Lead Nitrate, 0.01 M* in the test for *Limit of sodium chloride and sodium sulfate* under *Sodium Cetostearyl Sulfate*, which appears elsewhere in this number of *PF*.

(HDQ: M. Marques) RTS—39843-5

Add the following:

■**Methenamine**—Use *Methenamine* ⟨USP monograph⟩.■1S (*USP27*)

BRIEFING

Methoxyethanol, *USP 26* page 2478—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-58

Change to read:

Methoxyethanol (*Ethylene Glycol Monomethyl Ether; 2-Methoxyethanol*), $CH_3OCH_2CH_2OH$—**76.09**~~—Clear, colorless to slightly yellow liquid. Miscible with water, with acetone, with alcohol, with ether, with dimethylformamide, and with glycerin. Refractive index ($n20_D$): 1.420.[*Caution—Is poisonous; use with adequate ventilation.*]~~

~~*Specific gravity* ⟨841⟩: between 0.960 and 0.964.~~

~~*Boiling range* ⟨Reagent test⟩—Distil 100 mL: 95% distils between 123° and 126°.~~

~~*Acidity*—To 62 mL (60 g) add phenolphthalein TS, and titrate with 0.1 *N* alcoholic potassium hydroxide: not more than 1 mL is required to produce a pink endpoint that persists for not less than 15 seconds (0.01% as CH_3COOH).~~

~~*Dilution test*—Measure 10 mL into a glass-stoppered, 100-mL graduate. Dilute with water to 100 mL, insert the stopper, and mix: no haze or turbidity is observed after the mixture has been allowed to stand at room temperature for 2 hours.~~

~~*Water, Method I* ⟨921⟩: not more than 0.05%.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

2-Methoxyethanol, *USP 26* page 2478—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-59

Change to read:

2-Methoxyethanol (*Ethylene Glycol Monomethyl Ether; Methoxyethanol*), $CH_3OCH_2CH_2OH$—**76.09**~~—Clear, colorless to slightly yellow liquid. Miscible with water, with acetone, with alcohol, with ether, with dimethylformamide, and with glycerin. Refractive index (n^{20}_D): 1.420.[*Caution—Is poisonous; use with adequate ventilation.*]~~

~~*Specific gravity* ⟨841⟩: between 0.960 and 0.964.~~

~~*Boiling range* ⟨Reagent test⟩—Distill 100 mL: 95% distills between 123° and 126°.~~

~~*Acidity*—To 62 mL (60 g) add phenolphthalein TS, and titrate with 0.1 N alcoholic potassium hydroxide: not more than 1 mL is required to produce a pink endpoint that persists for not less than 15 seconds (0.01% as CH_3COOH).~~

~~*Dilution test*—Measure 10 mL into a glass-stoppered, 100-mL graduate. Dilute with water to 100 mL, insert the stopper, and mix: no haze or turbidity is observed after the mixture has been allowed to stand at room temperature for 2 hours.~~

~~*Water, Method I* ⟨921⟩: not more than 0.05%.~~

■—See *Methoxyethanol*.■1S (*USP27*)

BRIEFING

***p*-Methylaminophenol Sulfate,** *USP 26* page 2496—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-62

Change to read:

***p*-Methylaminophenol Sulfate,** $(p\text{-}CH_3NHC_6H_4OH)_2 \cdot H_2SO_4$—**344.38**~~—White, or yellow-white, small crystals or a crystalline powder. Discolors on exposure to air. Soluble in cold water; freely soluble in boiling water; slightly soluble in alcohol; insoluble in ether. Store in well-closed containers, protected from light.~~

~~*Solubility in HCl*—Add 100 mg to 2 mL of hydrochloric acid: it dissolves quickly and completely.~~

~~*o-Aminophenol*—To the solution from the preceding test add 1 drop of ferric chloride TS: no reddish brown color is produced.~~

~~*Residue on ignition* (Reagent test)—The residue from 2 g weighs not more than 2 mg (0.1%).~~

~~*Chloride*—To a solution of 1 g in 20 mL of water add 1 mL of nitric acid and 1 mL of silver nitrate TS: not more than a faint opalescence is produced.~~

~~*Suitability for phosphate test*—Dissolve 2 g in 100 mL of water. To 10 mL of this solution add 90 mL of water and 20 g of sodium bisulfite. Confirm the suitability of the reagent solution by the following test:~~

~~Add 1 mL of the reagent solution to each of four solutions containing 25 mL of 0.5 *N* sulfuric acid and 1 mL of a solution of 5 g ammonium molybdate in 100 mL of 1 *N* sulfuric acid. Add 0.005 mg of phosphate (PO_4) to one of the solutions, 0.01 mg to a second, and 0.02 mg to a third. Allow to stand at room temperature for 2 hours: the solutions in the three tubes show readily perceptible differences in blue color corresponding to the relative amounts of phosphate added, and the one to which 0.005 mg of phosphate was added is perceptibly a deeper blue than the blank.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Methyl Behenate, *USP 26* page 2494. It is proposed to include additional information regarding the temperature programming in the *Assay* test.

(HDQ: M. Marques) RTS—39883-1

Change to read:

Methyl Behenate, $C_{23}H_{46}O_2$—**354.61**—White powder.

Assay—Inject an appropriate specimen into a gas chromatograph (see *Chromatography* ⟨621⟩) equipped with a thermal conductivity detector, helium being used as the carrier gas. The following conditions have been found suitable: a 1.8-m × 2.0-mm glass column packed with 5% G3 phase on support S1A; the injection port temperature is maintained at 300°; the detector temperature is maintained at 300°;~~ the column temperature is maintained at 220° and programmed to rise 3° per minute to 220°.~~

■ the initial temperature of the oven is 220°, which is held for 2 minutes, and then programmed to rise 3° per minute to attain a final temperature of 270°, which is held for 10 minutes.■1S (*USP27*)

The area of the $C_{23}H_{46}O_2$ peak is not less than 98% of the total peak area.

Melting range ⟨741⟩: between 54° and 56°.

BRIEFING

Methyl Chloroform, *USP 26* page 2478—See briefing under Acetaldehyde.

(HDQ: M. Marques) RTS—39837-60

Change to read:

Methyl Chloroform (*Methylchloroform; 1,1,1-Trichloroethane*), CH_3CCl_3—**133.40**~~—Colorless, heavy liquid. Insoluble in water but is slightly hygroscopic. Miscible with alcohol, with ether, and with chloroform.~~

~~*Boiling range* (Reagent test)—Distil 100 mL: the difference between the temperatures observed when 1 and 95 mL have distilled does not exceed 1.6°. Its boiling temperature at 760 mm of Hg pressure is about 74°.~~

~~*Specific gravity* ⟨841⟩: between 1.312 and 1.321.~~

~~*Acidity*—Pipet 25 mL into 25 mL of alcohol neutralized to bromothymol blue TS with 0.02 *N* sodium hydroxide. Mix gently, and titrate with 0.020 *N* sodium hydroxide VS: not more than 0.50 mL is required to restore the blue color (0.001% as HCl).~~

~~*Residue on evaporation*—Evaporate 76 mL on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 1 mg (about 0.001%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Methyl Ethyl Ketone, *USP 26* page 2495—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-61

Change to read:

Methyl Ethyl Ketone, $CH_3COC_2H_5$—**72.11**~~—Colorless liquid, having an acetone-like odor. Soluble in water. Miscible with alcohol, with ether, and with benzene.~~

~~*Boiling range* (Reagent test): between 79.0° and 81.0°.~~

~~*Specific gravity* ⟨841⟩: between 0.801 and 0.803.~~

~~*Residue on evaporation*—Evaporate 50 mL on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 1.0 mg (0.0025%).~~

In-Process Revision

~~*Acidity*—Add 25 mL to 10 mL of 80 percent alcohol, previously neutralized to phenolphthalein TS with 0.02 *N* sodium hydroxide. Titrate with 0.020 *N* sodium hydroxide VS to the production of a pink color that persists for notless than 15 seconds: not more than 0.50 mL is consumed (0.003% as CH_3COOH).~~

~~*Solubility in water*—Add 5 mL to 40 mL of carbon dioxide-free water, and allow to stand for 20 minutes: the solution remains clear.~~

■—Use ACS reagent grade 2-Butanone.■1S (*USP27*)

BRIEFING

***N*-Methylpyrrolidine,** *USP 26* page 2496—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-63

Change to read:

▲***N*-Methylpyrrolidine** (1-*Methylpyrrolidine*), $C_4H_8NCH_3$—**85.15** [*120-94-5*]—Use~~a suitable grade.~~ ~~05~~ ▲*USP26*

■ACS reagent grade.■1S (*USP27*)

BRIEFING

Monochloroacetic Acid, *USP 26* page 2496—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-64

Change to read:

Monochloroacetic Acid,

■(*Chloroacetic Acid*, *Chloroethanoic Acid*)■1S (*USP27*)
$CH_2ClCOOH$—**94.50**—~~Colorless or white, deliquescent crystals, odorless in the cold. Very soluble in water; soluble in alcohol and in ether. Store in well-closed containers in a cool place.~~

~~*Assay*—Weigh accurately about 3 g, transfer to a suitable container, and dissolve in 50 mL of water. Add phenolphthalein TS, and titrate with 1 *N* sodium hydroxide VS. Each mL of 1 *N* sodium hydroxide is equivalent to 94.50 mg of $CH_2ClCOOH$. Not less than 99.0% is found.~~

~~*Melting range* ⟨741⟩: between 61.0° and 64.0°.~~

~~*Insoluble matter*: not more than 1.0 mg, from 10 g (0.010%).~~

~~*Residue on ignition* (Reagent test)—Ignite 5.0 g: the residue weighs not more than 1.0 mg (0.02%) (retain the residue).~~

~~*Chloride* (Reagent test)—One g shows not more than 0.01 mg of Cl (0.001%).~~

~~*Sulfate* (Reagent test, *Method I*)—One g shows not more than 0.2 mg of SO_4 (0.02%).~~

~~*Heavy metals* (Reagent test)—Test 2.0 g: the limit is 0.001%.~~

~~*Iron* ⟨241⟩—Digest the residue retained from the test for *Residue on ignition* with 6 mL of hydrochloric acid on a steam bath until solution is complete, then dilute with water to 150 mL. To 10 mL of the solution add 1.5 mL of hydrochloric acid, and dilute with water to 47 mL: the solution shows not more than 0.01 mg of Fe (0.003%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Monoethanolamine, *USP 26* page 2497—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-65

Change to read:

Monoethanolamine,

■(*2-Aminoethanol*)■1S (*USP27*)
C_2H_7NO—**61.08**—~~Clear, colorless to faintly yellow, viscous liquid having an ammoniacal odor. Miscible with water, with methanol, and with acetone. Melts at about 9°.~~

~~*Assay*—Weigh accurately a glass-stoppered weighing bottle containing 25 mL of water. Add about 2 g of test specimen, insert the stopper, and again weigh accurately. Add 3 drops of a mixed indicator prepared by adding 5 volumes of bromocresol green TS to 6 parts of methyl red TS (prepared from methyl red hydrochloride), and titrate with 1 *N* hydrochloric acid VS. Each mL of 1 *N* hydrochloric acid VS is equivalent to 61.08 mg of C_2H_7NO. Not less than 99% is found.~~

~~*Refractive index* ⟨831⟩: between 1.453 and 1.455 at 20°.~~

~~*Residue on ignition* ⟨281⟩—Evaporate 20 g on a steam bath to dryness, and ignite the residue at 800° ± 25° for 15 minutes: the residue weighs not more than 1 mg (0.005%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

2-Naphthyl Chloroformate, *USP 26* page 2497—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-66

Change to read:

2-Naphthyl Chloroformate (*Chloroformic Acid 2-Naphthyl Ester*), $ClCOOC_{10}H_7$—**206.62**—Use a suitable grade.~~45~~

■8■1S (*USP27*)

BRIEFING

Nitric Oxide–Nitrogen Dioxide Detector Tube, *USP 26* page 2498—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-67

Change to read:

Nitric Oxide–Nitrogen Dioxide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for an oxidizing layer and the indicator diphenyl benzidine. ~~[NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number CH 29401, Measuring Range 0.5 to 10 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.]~~

■*Measuring Range:* 0.5 to 10 ppm.[110] ■1S (*USP27*)

BRIEFING

Nitromethane, *USP 26* page 2498—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-68

Change to read:

Nitromethane, CH_3NO_2—**61.04**~~—Oily liquid. Soluble in water, in alcohol, in ether, and in dimethylformamide. Specific gravity: about 1.132. Water solutions are acid to litmus.~~

~~*Refractive index* ⟨831⟩: about 1.380 at 22°.~~

~~*Boiling range:* between 101° and 103°.~~

~~*Residue on evaporation:* negligible, from 50 mL.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Olefin Detector Tube, *USP 26* page 2499—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-69

Change to read:

Olefin Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator in a stabilized form of permanganate.

~~NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number CH 31201, Measuring Range 0.06 to 3.2 Vol. % Propylene, 0.04 to 2.4 Vol. % Butylene. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.~~

■*Measuring range:* 0.06 to 3.2 Vol.–% Propylene, 0.04 to 2.4 Vol.–% Butylene.[111] ■1S (*USP27*)

BRIEFING

Osmium Tetroxide, *USP 26* page 2499—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-70

Change to read:

Osmium Tetroxide (*Osmic Acid; Perosmic Anhydride*), OsO_4—**254.23**~~—Colorless or slightly yellow, hygroscopic crystals or crystalline granules. Very pungent odor. Decomposed by light. Slowly soluble in about 20 parts of water; soluble in alcohol and in ether, with decomposition. It softens at about 35°, melts between 40° and 42°, and boils at about 130°.~~

~~*Caution—Osmium Tetroxide vapors are poisonous and highly irritating to the eyes and to the respiratory membranes.*~~

~~*Solubility*—Dissolve 200 mg in 1 mL of carbon tetrachloride: a clear and not more than slightly yellow solution results, and no appreciable amount of insoluble residue remains.~~

~~*Nonvolatile matter*—Evaporate the solution remaining from the test for *Solubility* on a steam bath *in a well-ventilated hood* to dryness, and dry at 105° for 1 hour: the residue weighs not more than 0.4 mg (0.2%).~~

~~*Heavy metals*—To the residue from the test for *Nonvolatile matter* add 2 mL of hydrochloric acid, and evaporate the solution to dryness. Take up the residue in a few mL of water, dilute with water to 25 mL, and add 10 mL of hydrogen sulfide TS: any brown color produced is not darker than that of a control containing 0.01 mg of added Pb (0.005%).~~

■—Use ACS reagent grade.■1S (*USP27*)

In-Process Revision

BRIEFING

Periodic Acid, *USP 26* page 2501—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-71

Change to read:

Periodic Acid, H_5IO_6—**227.94**—White to pale yellow crystals. Very soluble in water. Undergoes slow decomposition to iodic acid.

~~*Assay*—Dissolve about 120 mg, accurately weighed, in water. Add 5 mL of hydrochloric acid and 5 g of potassium iodide, then add 3 mL of starch TS, and titrate the liberated iodine with 0.1 *N* sodium thiosulfate VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* sodium thiosulfate is equivalent to 2.849 mg of H_5IO_6. Not less than 99% is found.~~

~~*Insoluble matter* (Reagent test): not more than 1.0 mg, from 10.0 g (0.01%).~~

~~*Residue on ignition* (Reagent test): not more than 2 mg, from 10.0 g, ignited for 10 minutes (0.02%). [Retain for *Heavy metals* test.]~~

~~*Sulfate*—Weigh accurately 1 g, add 10 to 20 mg of anhydrous sodium carbonate, and evaporate to dryness three times with 5-mL portions of hydrochloric acid. Dissolve in 25 mL of water, add 1 mL of dilute hydrochloric acid (1 in 10), then add 1 mL of barium chloride TS, and compare the turbidity with that of *Standard Sulfate Solution* (See *Sulfate in Reagents*). One g shows not more than 0.1 mg of SO_4 (0.01%).~~

~~*Other halogens*—Dissolve 1.0 g in 100 mL of water, add 1 mL of phosphoric acid and 5 mL of 30 percent hydrogen peroxide, and boil to expel iodine. Dilute with water to 100 mL. To a 20-mL aliquot add 3 mL of nitric acid and 1 mL of silver nitrate TS. Compare the turbidity with that of a solution similarly prepared from a *Standard Chloride Solution* (See *Chloride in Reagents*) containing 0.02 mg of chloride (0.01%).~~

~~*Heavy metals*—To the *Residue on ignition* add several drops of acetic acid, and warm to dissolve. Transfer to a test tube and add 10 mL of hydrogen sulfide TS. Compare the color with that of *Standard Lead Solution* (See *Heavy Metals* ⟨231⟩) containing 0.5 mg of Pb (0.005%).~~

~~*Iron*—Dissolve 1.0 g in 50 mL of water, add 1 mL of dilute sulfuric acid (1 in 2) and 10 mL of hydroxylamine hydrochloride solution (1 in 5), and evaporate to dryness to expel iodine. Dissolve the residue in water, add 2 mL of 1,10-phenanthroline solution (1 in 1000) and 10 mL of sodium acetate solution (1 in 5), and compare the color with that of a solution containing 0.03 mg of iron, treated similarly (0.003%).~~

■Use ACS reagent grade.■1S (*USP27*)

BRIEFING

3-Phenoxybenzoic Acid, *USP 26* page 2502—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-72

Change to read:

3-Phenoxybenzoic Acid, $C_{13}H_{10}O_3$—**214.22** [*3739-38-6*]—Use a suitable grade.

Melting range ⟨741⟩: between 149° and 150°.~~92~~

■91■1S (*USP27*)

BRIEFING

2-Phenylacetamide, *USP 26* page 2502—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-73

Change to read:

2-Phenylacetamide (α-*Phenylacetamide*), C_8H_9NO—**135.16**

■[*103-81-1*]■1S (*USP27*)
—Bimorphous plates or leaflets. Slightly soluble in water. Use a suitable grade.~~1~~

■■1S (*USP27*)
Melting range ⟨741⟩: between 156° and 158°.

BRIEFING

Phenylglycine, *USP 26* page 2502—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-74

Change to read:

Phenylglycine (D(–)-*2-Phenylglycine*), ($C_6H_5CH(NH_2)COOH$)—**151.17** [*875-74-1*]—Use a suitable grade.~~52~~

■■1S (*USP27*)

BRIEFING

Phthalic Acid, *USP 26* page 2503—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-75

Change to read:

Phthalic Acid, $C_8H_6O_4$—**166.13**~~—Colorless to white crystalline powder. Soluble in alcohol and in methanol; slightly soluble in water; practically insoluble in chloroform.~~

~~*Assay*—Transfer about 2.8 g, accurately weighed, to a 250-mL conical flask, and add 50.0 mL of 1 *N* sodium hydroxide VS. Add 25 mL of water, and warm on a hot plate until solution is complete. Add phenolphthalein TS, and titrate the excess sodium hydroxide with 1 *N* sulfuric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 1 *N* sodium hydroxide is equivalent to 83.06 mg of $C_8H_6O_4$. Not less than 98% is found.~~

~~*Melting range* ⟨741⟩: between 205° and 209°, with decomposition, a sealed capillary tube being used.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Potassium Dichromate, *USP 26* page 2504—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-76

Change to read:

Potassium Dichromate, $K_2Cr_2O_7$—**294.18**—Use ACS reagent grade. [NOTE—Potassium dichromate of a quality suitable as a primary standard is available from the National Institute of Standards and Technology, Washington, DC ~~20234,~~

■, www.nist.gov,■1S (*USP27*)
as standard sample ~~No. 136a.~~

■No. 136.]■1S (*USP27*)

BRIEFING

Potassium Phosphate, Monobasic, *USP 26* page 2504—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-77

Change to read:

Potassium Phosphate, Monobasic (*Potassium Biphosphate; Potassium Dihydrogen Phosphate*), KH_2PO_4—**136.09**—Use ACS reagent grade. [NOTE—Certified Potassium Dihydrogen Phosphate is available from the National Institute of Standards and Technology, Washington, DC ~~20234,~~

■, www.nist.gov,■1S (*USP27*)
as standard sample ~~No. 186-I.~~

■No. 186.]■1S (*USP27*)

BRIEFING

Potassium Phosphate, Tribasic, *USP 26* page 2504—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-78

Change to read:

Potassium Phosphate, Tribasic, K_3PO_4—**212.27**—Deliquescent, orthorhombic crystals. Use ~~a suitable grade.~~

■ACS reagent grade.■1S (*USP27*)

BRIEFING

***n*-Propyl Alcohol,** *USP 26* page 2505—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-79

Change to read:

***n*-Propyl Alcohol** (*1-Propanol*), $CH_3CH_2CH_2OH$—**60.10**~~—Clear, colorless liquid, having an ethanol like odor. Miscible with water and with most organic solvents. Specific gravity: about 0.803.~~

~~*Boiling range* (Reagent test)—Not less than 95% distils between 95° and 98°.~~

In-Process Revision

~~*Residue on evaporation*—Evaporate 25 mL (20 g) on a steam bath, and dry at 105° for 1 hour: the residue weighs not more than 1 mg (0.005%).~~

~~*Acidity*—Add 0.2 mL of phenolphthalein TS to 20 mL of water, and titrate with 0.1 *N* sodium hydroxide until a slight pink color persists after shaking. Add 10 mL of the alcohol, and titrate with 0.10 *N* sodium hydroxide: not more than 0.20 mL is required to restore the pink color (about 0.015% as CH_3COOH).~~

~~*Alkalinity*—Add 2 drops of methyl red TS to a solution of 6 mL in 25 mL of carbon dioxide–free water, and titrate with 0.02 *N* sulfuric acid: not more than 0.3 mL is required to produce a red color (about 0.002% as NH_3).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Protein Molecular Weight Standard. This new reagent is used in the test for *Content of 83 kDa protein* in the proposed monograph *Anthrax Vaccine Adsorbed*.

(HDQ: M. Marques) RTS—39998-5

Add the following:

■**Protein Molecular Weight Standard**—Also known as protein molecular weight markers (for SDS-PAGE) and consists of a mixture of several proteins of well-defined molecular weights. The products are generally available in a suitable buffer containing a suitable reducing agent (generally, 100 mM DDT), a preservative (for example, sodium azide), and 50% glycerol to prevent freezing. Use a suitable grade. Store at –20°.■1S (*USP27*)

BRIEFING

Sodium 1-Decanesulfonate, *USP 26* page 2511—See briefing under Acetaldehyde.

(HDQ: M. Marques) RTS—39837-85

Change to read:

Sodium 1-Decanesulfonate—Use a suitable grade.[74]

■■1S (*USP27*)

BRIEFING

Sodium Acetate, *USP 26* page 2508—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-80

Change to read:

Sodium Acetate, $NaC_2H_3O_2 \cdot 3H_2O$—**136.08**—Use ACS reagent grade

■Sodium Acetate Trihydrate.■1S (*USP27*)

BRIEFING

Sodium Acetate, Anhydrous, *USP 26* page 2508—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-81

Change to read:

Sodium Acetate, Anhydrous, $NaC_2H_3O_2$—**82.03**~~—Grayish white masses or powder. Hygroscopic. Freely soluble in water.~~

~~*Loss on drying* ⟨731⟩—Dry it at 120° to constant weight: it loses not more than 3.0% of its weight.~~

~~*Neutrality*—Dissolve 5 g in 100 mL of carbon dioxide–free water, cool to 10°, and add phenolphthalein TS. If a pink color is produced, it is discharged by the addition of not more than 0.50 mL of 0.020 *N* hydrochloric acid. If no pink color is produced, the addition of 0.50 mL of 0.020 *N* sodium hydroxide produces a pink color (about 0.02% of alkali as Na_2CO_3, or about 0.012% of acid as CH_3COOH).~~

~~*Chloride* (Reagent test)—One g shows not more than 0.1 mg of Cl (0.01%).~~

~~*Heavy metals* (Reagent test): 0.0015%.~~

~~*Sulfate* (Reagent test, *Method I*)—One g shows not more than 0.2 mg of SO_4 (0.02%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Sodium Arsenite, Twentieth-Molar (0.05 M). It is proposed to add this new volumetric solution.

(HDQ: M. Marques) RTS—39804-1

Add the following:

■Sodium Arsenite, Twentieth-Molar (0.05 M)
$NaAsO_2$ **129.91**

6.496 g in 1000 mL

Transfer 4.9455 g of arsenic trioxide, which has been pulverized and dried at 100° to constant weight, to a 1000-mL volumetric flask, dissolve it in 40 mL of 1 N sodium hydroxide, and add 1 N sulfuric acid or 1 N hydrochloric acid until the solution is neutral or only slightly acid to litmus. Add 30 g of sodium bicarbonate, dilute with water to volume, and mix.■1S (*USP27*)

BRIEFING

Sodium Borate, *USP 26* page 2510—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-82

Change to read:

Sodium Borate (*Borax; Sodium Tetraborate*), $Na_2B_4O_7 \cdot 10H_2O$—**381.37**—Use ACS reagent grade. [NOTE—Certified Borax is available from the National Institute of Standards and Technology, Washington, DC, ~~20234~~

■www.nist.gov,■1S (*USP27*) as standard sample No. 187.]

BRIEFING

Sodium Bromide, *USP 26* page 2510—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-83

Change to read:

Sodium Bromide, NaBr—**102.89**~~—White, odorless, cubical crystals or granular powder. Soluble in water; slightly soluble in alcohol.~~

~~*Insoluble matter* (Reagent test)—The insoluble matter from 20 g, dissolved in 150 mL of hot water, weighs not more than 1 mg (0.005%).~~

~~*pH* ⟨791⟩: between 5.5 and 7.5, in a solution (1 in 20).~~

~~*Barium*—Dissolve 6 g in 15 mL of water, add 5 mL of acetic acid, 5 mL of 30 percent hydrogen peroxide, and 1 mL of hydrochloric acid, and digest in a covered beaker until the reaction ceases. Remove the cover, and evaporate to dryness. Dissolve the residue in 15 mL of water, filter if necessary, dilute with water to 23 mL, and add 2 mL of potassium dichromate solution (1 in 10). Add ammonium hydroxide until the orange color has been dissipated and the yellow color persists, then add 25 mL of methanol, stir vigorously, and allow to stand for 10 minutes: any turbidity produced does not exceed that of a control containing 1.0 g of test specimen and 100 µg of added barium ion (0.002%).~~

~~*Bromate*—Dissolve 1 g in 10 mL of oxygen-free water, add 100 µL of potassium iodide solution (1 in 10), 1 mL of starch TS, and 25 µL of dilute sulfuric acid (1 in 36), and allow to stand at 25°: no blue or violet color is produced within 10 minutes (about 0.001%).~~

~~*Calcium, magnesium,* and R_2O_3 *precipitate*—To the filtrate from the test for *Insoluble matter* add 5 mL of ammonium oxalate TS, 2 mL of ammonium phosphate TS, and 10 mL of ammonium hydroxide. Allow to stand for about 16 hours, filter, wash with dilute ammonia TS (1 in 4), ignite, and weigh: the weight of the residue is not more than 1 mg (0.005%).~~

~~*Chloride*—Dissolve 500 mg in 15 mL of dilute nitric acid (1 in 3) in a small conical flask, add 3 mL of 30 percent hydrogen peroxide, and digest on a steam bath until the solution is colorless. Wash down the sides of the flask with a small quantity of water, digest for an additional 15 minutes, cool, and dilute with water to 200 mL. Dilute a 2 mL aliquot with water to 25 mL, and add 1 mL of nitric acid and 1 mL of silver nitrate TS: any turbidity produced does not exceed that of a control containing 10 µg of added chloride ion (0.2%).~~

~~*Heavy metals* (Reagent test): 0.0005%.~~

~~*Iron* ⟨241⟩—Two g, dissolved in 47 mL of water containing 2 mL of hydrochloric acid, shows not more than 0.01 mg of Fe (5 ppm).~~

~~*Nitrogen compounds* (Reagent test)—One g shows not more than 5 µg of N (0.0005%).~~

~~*Potassium* (Reagent test)—~~

~~TEST SOLUTION—Dissolve 10 g in water, dilute with water to 100 mL, and mix.~~

~~SAMPLE SOLUTION—Dilute 10.0 mL of *Test solution* with water to 100 mL, and mix.~~

~~CONTROL SOLUTION—To 10.0 mL of *Test solution* add 50 µg of potassium ion (K), dilute with water to 100 mL, and mix. The limit is 0.005%.~~

~~*Sulfate*—Dissolve 10 g in 100 mL of water, filter if necessary, and add 1 mL of hydrochloric acid: the solution yields not more than 1.2 mg of residue (0.005%).~~

■—Use ACS reagent grade.■1S (*USP27*)

In-Process Revision

BRIEFING

Sodium Dichromate, *USP 26* page 2510—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-84

Change to read:

Sodium Dichromate, $Na_2Cr_2O_7 \cdot 2H_2O$ (for chromic acid cleaning mixture)—**298.00**~~— Orange-red crystals or granules. Very soluble in water; insoluble in alcohol.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Sodium Oxalate, *USP 26* page 2511—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-86

Change to read:

Sodium Oxalate, $Na_2C_2O_4$—**134.00**—Use ACS reagent grade. [NOTE—Sodium Oxalate of a quality suitable as a primary standard is available from the Office of Standard Reference Materials, National Institute of Standards and Technology, Washington, DC,~~ 20234,~~

■www.nist.gov,■1S (*USP27*)
as standard sample ~~No. 40g.~~

■No. 40.]■1S (*USP27*)

BRIEFING

Sodium Perchlorate, *USP 26* page 2512—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-87

Change to read:

Sodium Perchlorate, $NaClO_4 \cdot H_2O$—**140.46**~~— Colorless, deliquescent crystals. Decomposes at about 150°. Soluble in 95% alcohol.~~

~~*Assay*— Dry about 1.5 g in a vacuum desiccator at 80° to constant weight. Mix 750 mg, accurately weighed, of the dried and powdered test specimen with 5 g of powdered sodium nitrite in a nickel crucible, cover the crucible, and heat it over a free flame until the mixture is well melted. Maintain it in this state, without raising the temperature much higher, for 30 minutes. Allow to cool, add 20 mL of hot water, and digest until the melt is dissolved. Filter into a 200-mL volumetric flask, wash any undissolved matter thoroughly with hot water, cool, dilute with water to volume, and mix.~~

~~Transfer 50.0 mL of the solution to a 250-mL, glass-stoppered flask, add 25.0 mL of 0.1 *N* silver nitrate VS, then add slowly 6 mL of dilute nitric acid (1 in 6), and heat on the steam bath to expel oxides of nitrogen. Cool, add 3 mL of nitrobenzene, shake well for 1 to 2 minutes, then add 4 mL of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 *N* silver nitrate is equivalent to 12.24 mg of $NaClO_4$: not less than 98.0% of $NaClO_4$ is found.~~

~~*Insoluble matter*— Dissolve 10 g in 50 mL of water, heat to boiling, and filter through a tared sintered-glass crucible. Wash well with water, rinsing the beaker thoroughly. Dry at 105° for 2 hours, and weigh. The weight of the insoluble residue does not exceed 1 mg (0.01%).~~

~~*Chlorate and chloride* (*as Cl*)— Dissolve 1 g in 10 mL of water, add 1 mL of 0.1 *N* ferrous sulfate, and heat on the steam bath for 15 minutes. Cool, dilute with water to 50 mL, and add 1 mL of nitric acid and 1 mL of silver nitrate TS. Any turbidity does not exceed that produced by 0.1 mg of chloride (Cl) contained in a similarly treated blank (0.01% of Cl).~~

~~*Sulfate*— Dissolve 1 g in 10 mL of water, and add 0.05 mL of diluted hydrochloric acid and 1 mL of barium chloride TS. Any turbidity produced in 10 minutes does not exceed that produced in a blank containing 0.05 mg of added SO_4 (0.005%).~~

~~*Calcium*— Dissolve 500 mg in 10 mL of hot water, add 0.25 mL of ammonia TS and 3 mL of ammonium oxalate TS, and keep the solution hot. No turbidity is produced in 5 minutes (about 0.02%).~~

~~*Heavy metals* (Reagent test)— Dissolve 1 g in 25 mL of water: the heavy metals limit is 0.002%.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Sodium Pyrophosphate, *USP 26* page 2512—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-88

Change to read:

Sodium Pyrophosphate, ~~$Na_4P_2O_7$~~

■ $Na_4P_2O_7 \cdot 10H_2O$■1S (*USP27*)
—**265.90**—Use ACS reagent grade.

BRIEFING

Sodium Sulfate, *USP 26* page 2512—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-89

Change to read:

Sodium Sulfate (*Glauber's Salt*), $Na_2SO_4 \cdot 10H_2O$—**322.20—** ~~Colorless, odorless crystals or white granules. Is efflorescent. Melts at 32.5°. Soluble in 1.5 parts of water; soluble in glycerin; insoluble in alcohol. Store in well-closed containers, protected from heat.~~

~~*Insoluble matter* (Reagent test): not more than 1 mg, from 10 g (0.01%).~~

~~*pH*—The pH of a solution of 10 g in 200 mL of ammonia-free and carbon dioxide-free water is between 5.2 and 8.2.~~

~~*Arsenic* (Reagent test)—The stain produced by 3 g does not exceed that produced by 0.003 mg of As (1 ppm).~~

~~*Calcium, magnesium, and R_2O_3 precipitate*—Dissolve 5 g in 75 mL of water, filter, and add 5 mL of ammonium oxalate TS, 2 mL of ammonium phosphate TS, and 10 mL of ammonium hydroxide. Stir well, and allow to stand overnight. If any precipitate forms, filter, wash with dilute ammonia TS (1 in 4), and ignite: the residue weighs not more than 1 mg (0.02%).~~

~~*Chloride*—Dissolve 1 g in 50 mL of water, and filter if necessary. To 25 mL of the solution add 1 mL of nitric acid and 1 mL of silver nitrate TS: any turbidity produced does not exceed that of a control containing 0.01 mg of Cl (0.002%).~~

~~*Heavy metals* (Reagent test): 5 ppm.~~

~~*Iron* ⟨241⟩—One g, dissolved in 47 mL of water containing 2 mL of hydrochloric acid, shows not more than 0.01 mg of Fe (0.001%).~~

~~*Nitrogen compounds* (Reagent test)—Two g shows not more than 0.01 mg of N (5 ppm).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Sodium Tetraphenylborate—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-90

Add the following:

■**Sodium Tetraphenylborate,** $NaB(C_6H_5)_4$—**342.22**—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Starch, Soluble, Purified, *USP 26* page 2513—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-91

Change to read:

Starch, Soluble, Purified ~~76~~

■■1S (*USP27*)
—White, amorphous powder; under microscopic examination it shows the characteristic form of potato starch. Soluble in hot water; very slightly soluble in alcohol.

TEST SOLUTION FOR DETERMINATION OF PH AND SENSITIVITY—Stir 2.0 g in 10 mL of water, add boiling water to make 100 mL, and boil for 2minutes. The hot solution is almost clear. On cooling, the solution may become opalescent or turbid, but does not gel. Use it as the *Test solution*.

pH ⟨791⟩—The pH of the *Test solution* is between 6.0 and 7.5.

Sensitivity—Mix 2.5 mL of *Test solution*, 97.5 mL of water, and 0.50 mL of 0.010 N iodine: a distinct blue color results, and it disappears upon the addition of 0.50 mL of 0.010 N sodium thiosulfate.

Absorbance—Prepare a pH 5.3 buffer solution by dissolving 43.5 g of sodium acetate (trihydrate) and 4.5 mL of glacial acetic acid in water, transferring the resultant solution to a 250-mL volumetric flask, adding water to volume, and mixing.

Dissolve 1.00 g of Soluble, Purified Starch in 2.5 mL of the buffer solution by warming, transfer to a 100-mL volumetric flask, add water to volume, and mix. Add 0.50 mL of this solution to a 100-mL volumetric flask containing about 75 mL of water, 1 mL of 1 N hydrochloric acid, and 1.5 mL of 0.020 N iodine, swirling the flask during the addition. Add water to volume, mix, and allow to stand in the dark for 1 hour. The absorbance of this solution, measured at 575 nm in a 1-cm cell against a blank, is between 0.5 and 0.6.

Reducing substances—Shake 10.0 g with 100 mL of water for 15 minutes, and allow to settle for about 12 hours. Filter a portion of the supernatant through fine sintered glass. To 50 mL of the filtrate add 50 mL of alkaline cupric tartrate TS, and boil for 1 to 2 minutes. Filter the resulting cuprous oxide, wash it with hot water and then with alcohol, and dry it at 105° for 2 hours: not more than 47 mg is found, corresponding to 0.7% of reducing sugars as maltose.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 10% of its weight.

Residue on ignition ⟨281⟩: not more than 0.5%.

In-Process Revision

BRIEFING

Succinic Acid, *USP 26* page 2514—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-92

Change to read:

Succinic Acid, $C_4H_6O_4$—**118.09** [*771-50-6*]—Use ~~a suitable grade.~~

■ACS reagent grade.■1S (*USP27*)

BRIEFING

Sulfamic Acid, *USP 26* page 2514—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-93

Change to read:

Sulfamic Acid, HSO_3NH_2—**97.09**~~—Colorless or white crystals. Soluble in water; slightly soluble in alcohol.~~

~~*Assay*—Weigh accurately about 400 mg, previously dried over sulfuric acid for 2 hours, and dissolve in 30 mL of water contained in a small flask. Add phenolphthalein TS, and titrate with 0.1 *N* sodium hydroxide VS. Each mL of 0.1 *N* sodium hydroxide consumed is equivalent to 9.709 mg of HSO_3NH_2. Not less than 99.5% is found.~~

~~*Insoluble matter* (Reagent test): not more than 1 mg, from 10 g dissolved in 200 mL of water (0.01%).~~

~~*Residue on ignition* (Reagent test)—Ignite 5 g: the residue weighs not more than 0.5 mg (0.01%).~~

~~*Chloride* (Reagent test)—One g shows not more than 0.01 mg of Cl (0.001%).~~

~~*Heavy metals*—Dissolve 4 g in 30 mL of water, neutralize with stronger ammonia water to litmus, and dilute with water to 40 mL. To 30 mL add 2 mL of diluted acetic acid, dilute with water to 40 mL, and add 10 mL of hydrogen sulfide TS: any brown color produced is not darker than that of a control containing the remaining 10 mL of test solution and 0.02 mg of added Pb (0.001%).~~

~~*Iron* ⟨241⟩—Two g, dissolved in 47 mL of water containing 2 mL of hydrochloric acid, shows not more than 0.01 mg of Fe (5 ppm).~~

~~*Sulfate* (Reagent test, *Method I*)—Dissolve 1 g in 50 mL of water: 20 mL of the solution shows not more than 0.2 mg of SO_4 (0.05%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Sulfur Dioxide Detector Tube, *USP 26* page 2515—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-94

Change to read:

Sulfur Dioxide Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for an iodine-starch indicator. ~~[NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number CH 31701, Measuring Range 1 to 25 ppm. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices*.]~~

■*Measuring range:* 1 to 25 ppm.[110]■1S (*USP27*)

BRIEFING

Tannic Acid *(Tannin), USP 26* page 2515—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-95

Change to read:

Tannic Acid (*Tannin*)~~—Yellowish to light brown, glistening scales, or an amorphous powder. Is odorless or has a faint, characteristic odor. Very soluble in water and in alcohol; less soluble in dehydrated alcohol. Soluble in acetone; practically insoluble in benzene, in chloroform, and in ether. Store in light-resistant containers.~~

~~*Solubility*—A solution of 2 g in 10 mL of water is clear or practically so.~~

~~*Residue on ignition* (Reagent test)—Ignite 1 g with 1 mL of sulfuric acid: the residue weighs not more than 1 mg (0.1%).~~

~~*Loss on drying* ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 12% of its weight.~~

~~*Dextrin, gum, and resinous substances*—Dissolve 2 g in 10 mL of warm water: the solution is clear or not more than faintly turbid. Filter if necessary, and divide the filtrate into two equal portions. To one portion add 10 mL of alcohol. To the other portion add 10 mL of water: no turbidity is produced in either solution.~~

~~*Heavy metals*—To the *Residue on ignition* add 1 mL each of hydrochloric acid and nitric acid, and evaporate on a steam bath to dryness. Take up with 1 mL of 1 *N* hydrochloric acid and a few mL of hot water, dilute with water to 40 mL, and add 10 mL of hydrogen sulfide TS: any brown color produced is not darker than that of a control containing 0.02 mg of added Pb (0.002%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

2′,4′,5′,7′-Tetrabromofluorescein. This new reagent is to be used in the *Benzethonium chloride* test in the proposed monograph *Anthrax Vaccine Adsorbed.*

(HDQ: M. Marques) RTS—39998-6

Add the following:

■**2′,4′,5′,7′-Tetrabromofluorescein** (*Eosin Y, Eosin Yellowish*, *Eosin Bromo ES*, *Solvent Red 43*, *Acid Red 87*), $C_{20}H_8Br_4O_5$—**167.8** [*630-20-6*]—Dark red to brown powder. Solubility 0.1% in water (clear orange solution). Use a suitable grade.■1S (*USP27*)

BRIEFING

Tetrabutylammonium Bromide, *USP 26* page 2515—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-96

Change to read:

Tetrabutylammonium Bromide, $(C_4H_9)_4NBr$—**322.37**—~~White crystalline powder.~~

~~*Assay*~~ ~~Dissolve about 34 mg, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 *N* perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary corrections. Each mL of 0.1 *N* perchloric acid is equivalent to 32.24 mg of $(C_4H_9)_4NBr$. Not less than 99% is found.~~

~~*Melting range* ⟨741⟩: between 103° and 105°.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

1,1,2,2-Tetrachloroethane. This new reagent is to be used in the *Benzethonium chloride* test in the proposed monograph *Anthrax Vaccine Adsorbed.*

(HDQ: M. Marques) RTS—39998-7

Add the following:

■**1,1,2,2-Tetrachloroethane,** $C_2H_2Cl_4$—**167.8** [*630-20-6*]—Colorless clear liquid. Specific gravity: 1.553. Refractive index at 20° is 1.481. Use a suitable grade.■1S (*USP27*)

BRIEFING

Tetrahydrofuran, *USP 26* page 2516—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-97

Change to read:

Tetrahydrofuran, C_4H_8O—**72.11**—~~Colorless liquid, having a characteristic, pungent odor. Miscible with water and with common organic solvents. When mixed with water, generates some heat and shrinks in volume; when mixed with chloroform, generates considerable heat. The name and concentration of any suitable preservative, not exceeding 0.1%, added to prevent formation of peroxides, are stated on the label. Preserve in small, well-filled containers, protected from light.~~

~~*Specific gravity* ⟨841⟩: between 0.884 and 0.886.~~

~~*Distilling range*, *Method II* ⟨721⟩: between 65° and 66°.~~

~~*Acidity*~~ ~~Mix 5.0 mL with 10 mL of water and 1 drop of methyl red TS: any pink color produced is changed to yellow by addition of not more than 0.25 mL of 0.020 *N* sodium hydroxide.~~

~~*Water*, *Method I* ⟨921⟩: not more than 0.1%.~~

~~*Residue on evaporation*~~ ~~Evaporate 10 mL (12 g) on a steam bath to dryness, and dry the residue at 105° for 1 hour: the weight of the residue is not more than 2 mg if a preservative is present, or not more than 1 mg if no preservative is declared on the label.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Tetrahydrofuran, Stabilizer-Free, *USP 26* page 2516—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-98

Change to read:

Tetrahydrofuran, Stabilizer-Free—Use a suitable grade.[79]

■■1S (*USP27*)

In-Process Revision

BRIEFING

Tetramethylammonium Bromide, *USP 26* page 2516—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-99

Change to read:

Tetramethylammonium Bromide, $(CH_3)_4NBr$—**154.05**—~~Colorless crystals. Soluble in water; sparingly soluble in absolute alcohol; insoluble in chloroform and in ether.~~

~~*Assay*—Transfer about 400 mg, accurately weighed, to a beaker, add 50 mL of water and 10 mL of diluted nitric acid, swirl to dissolve the test specimen, add 50.0 mL of 0.1 *N* silver nitrate VS, and mix. Add 2 mL of ferric ammonium sulfate TS, and titrate the excess silver nitrate with 0.1 *N* ammonium thiocyanate VS: each mL of 0.1 *N* silver nitrate consumed is equivalent to 15.41 mg of $(CH_3)_4NBr$. Not less than 98% is found.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Thiourea, *USP 26* page 2517—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-100

Change to read:

Thiourea, $(NH_2)_2CS$—**76.12**—~~White, odorless crystals or a white, crystalline powder. Soluble in water and in alcohol.~~

~~*Assay*—Weigh accurately 1 g, transfer to a 250 mL volumetric flask, dissolve in 50 mL of water, and dilute with water to volume. Pipet 20 mL of the well-mixed solution into a suitable flask, and add 25.0 mL of 0.1 *N* silver nitrate VS and 10 mL of ammonia TS. Shake vigorously for 2 minutes, heat to boiling, and cool. Add 60 mL of diluted nitric acid, shake vigorously, filter, and wash the residue well with water. Add 2 mL of ferric ammonium sulfate TS to the combined filtrate and washings, and titrate with 0.1 *N* ammonium thiocyanate VS. Each mL of 0.1 *N* silver nitrate consumed is equivalent to 3.806 mg of $(NH_2)_2CS$. Not less than 99% is found.~~

~~*Solubility*—A solution of 1 g in 20 mL of water is complete, clear, and colorless.~~

~~*Melting range, Method I* ⟨741⟩: between 176° and 182°.~~

~~*Loss on drying* ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.~~

~~*Residue on ignition* (Reagent test)—Ignite 1 g with 0.5 mL of sulfuric acid: the residue weighs not more than 1.5 mg (0.15%).~~

~~*Sensitiveness*—Dissolve 280 mg of bismuth subnitrate in 12 mL of nitric acid, and dilute with water to 200 mL. Dilute 1 mL of this solution with water to 100 mL, and to 10 mL of the dilution add 1 mL of test solution (1 in 5): a distinct yellow color is produced immediately.~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

***p*-Toluenesulfonic Acid,** *USP 26* page 2518—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-101

Change to read:

***p*-Toluenesulfonic Acid,** $CH_3C_6H_4SO_3H \cdot H_2O$—**190.22**—~~White, hygroscopic crystals or crystalline powder. Soluble in water, in alcohol, and in ether.~~

~~*Assay*—Weigh accurately about 5 g, previously dried over sulfuric acid for 18 hours, and dissolve in about 250 mL of water contained in a 500-mL conical flask. Add 0.15 mL of bromothymol blue TS, and titrate with 1 *N* sodium hydroxide VS to a blue end-point. Each mL of 1 *N* sodium hydroxide is equivalent to 190.2 mg of $CH_3C_6H_4SO_3H \cdot H_2O$. Not less than 99% is found.~~

~~*Melting range* ⟨741⟩: between 104° and 106°, the test specimen having been dried over sulfuric acid for 18 hours.~~

~~*Loss on drying* ⟨731⟩—Dry it over sulfuric acid to constant weight: it loses not more than 1% of its weight.~~

~~*Solubility*—Separate 200-mg portions dissolve completely in 5 mL of alcohol and in 5 mL of ether, respectively.~~

~~*Residue on ignition* ⟨281⟩: negligible, from 200 mg.~~

~~*Free sulfate*—Dissolve 500 mg in 10 mL of water, and add 1 mL of dilute hydrochloric acid (1 in 20) and 1 mL of barium chloride TS: any turbidity produced within 10 minutes does not exceed that of a control containing 0.05 mg of added SO_4 (0.01%).~~

■—Use ACS reagent grade.■1S (*USP27*)

BRIEFING

Trichlorotrifluoroethane, *USP 26* page 2518—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-102

Change to read:

Trichlorotrifluoroethane—Use ~~a suitable grade.~~[80]

■ACS reagent grade.■1S (*USP27*)

BRIEFING

Water Vapor Detector Tube, *USP 26* page 2521—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-103

Change to read:

Water Vapor Detector Tube—A fuse-sealed glass tube so designed that gas may be passed through it and containing suitable absorbing filters and support media for the indicator, which consists of a selenium sol in suspension in sulfuric acid. ~~[NOTE—A suitable detector tube that conforms to the monograph specification is available from Draeger Safety, Inc., P.O. Box 120, Pittsburgh, PA 15230-0120 as Reference Number 67 28531, Measuring Range 5 to 250 mg per cubic meter. Tubes having conditions other than those specified in the monograph may be used in accordance with the section entitled *Tests and Assays* in the *General Notices and Requirements*.]~~

■*Measuring range:* 5 to 250 mg per cubic meter.[110] ■1S (*USP27*)

BRIEFING

Zinc Acetate, *USP 26* page 2522—See briefing under *Acetaldehyde*.

(HDQ: M. Marques) RTS—39837-104

Change to read:

Zinc Acetate, $Zn(CH_3COO)_2 \cdot 2H_2O$—**219.51**~~—Colorless crystals or white, crystalline plates, having a slight odor of acetic acid. A 1-g portion dissolves in about 2.5 mL of water and in about 30 mL of alcohol.~~

~~*Insoluble matter* (Reagent test)—Twenty g, dissolved in 200 mL of water and 2 mL of glacial acetic acid, shows not more than 1.0 mg of insoluble matter (0.005%).~~

~~*Chloride* (Reagent test)—Two g shows not more than 0.01 mg of Cl (5 ppm).~~

~~*Nitrate*—Dissolve 1 g in 10 mL of water and 50 µL of indigo carmine TS, and then add 10 mL of sulfuric acid: the blue color persists for 5 minutes (about 0.005%).~~

~~*Sulfate* (Reagent test, *Method II*)—Dissolve 20 g in 200 mL of water, add 1 mL of hydrochloric acid, and filter: the filtrate, 10 mL of barium chloride TS being used, yields not more than 1.0 mg of residue (0.002% as SO_4).~~

~~*Alkalies and earths*—Dissolve 2 g in 140 mL of water, add 10 mL of stronger ammonia TS, completely precipitate the zinc with hydrogen sulfide, and filter. To 75 mL of the filtrate add 5 drops of sulfuric acid, evaporate, and ignite: the residue weighs not more than 1 mg (0.1%).~~

~~*Arsenic* ⟨211⟩—Dissolve 6 g in water: the limit is 0.5 ppm.~~

~~*Iron* ⟨241⟩—Dissolve 2 g in 45 mL of water, and add 2 mL of hydrochloric acid: the solution shows not more than 0.01 mg (5 ppm).~~

~~*Lead* ⟨251⟩—Dissolve 1 g in 20 mL of water. To 5 mL of the solution add 0.02 mg of Pb and 12 mL of potassium cyanide solution (3 in 20), and dilute with water to 50 mL (*A*). To the remaining 15 mL add 12 mL of the potassium cyanide solution, and dilute to 50 mL with water (*B*). Then to each add 5 drops of sodium sulfide TS: *B* is not darker than *A* (0.004%).~~

■—Use ACS reagent grade.■1S (*USP27*)

VOLUMETRIC SOLUTIONS

BRIEFING

Lead Nitrate, Hundredth-Molar (0.01 M). This new volumetric solution is used in the test for *Limit of sodium chloride and sodium sulfate* under *Sodium Cetostearyl Sulfate*, which appears elsewhere in this number of *PF*.

(HDQ: M. Marques) RTS—39843-4

Change to read:

■**Lead Nitrate, Hundredth-Molar (0.01 M)**
$Pb(NO_3)_2$, **331.21**

3.312 g in 1000 mL

Xylenol Orange Triturate—Triturate 1 part of xylenol orange with 99 parts of potassium nitrate.

0.1 M Lead Nitrate—Dissolve 33 g of lead nitrate in 1000 mL of water. Standardize the solution as follows. To 20.0 mL of the lead nitrate solution add 300 mL of water. Add about 50 mg of *Xylenol Orange Triturate*, and add methenamine until the solution becomes violet-pink. Titrate with 0.1 M edetate disodium VS to the yellow endpoint. Calculate the molarity.

Dilute 50.0 mL of *0.1 M Lead Nitrate* to 500.0 mL with water.■1S (*USP27*)

In-Process Revision

BRIEFING

Reagent Footnotes, *USP 26* page 2538, page 3013 of the *First Supplement*, page 3373 of *PF* 27(6) [Nov.–Dec. 2001], page 553 of *PF* 28(2) [Mar.–Apr. 2001], page 1952 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], and page 508 of *PF* 29(2) [Mar. –Apr. 2003]. An extensive revision to items in the *Reagent Specifications* and *Reagent Footnotes* sections is made to provide a more consistent and user-friendly document. Some obsolete reagents and their respective footnotes are deleted; and, to the extent possible, specifications are harmonized with the American Chemical Society Reagent Specifications. Also, the contact information for possible suppliers is updated. See briefing under Acetaldehyde, which appears elsewhere in this number of *PF*.

(HDQ: M. Marques) RTS—39837-1

Reagent Footnotes

Change to read:

[1] A suitable grade is available as β-(Acetylmercapto)isobutyric Acid, catalog number 39059, from Senn Chemicals AG ~~P.O. Box 267, CH-8157 Dielsdorf, Switzerland.~~

■www.sennchem.com.■1S (*USP27*)

Change to read:

[2] A suitable grade is available commercially as "Triton X-100" from ~~Rohm and Haas Co., Philadelphia, PA 19105.~~

■Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Delete the following:

■~~[3] A suitable grade is basic aluminum oxide, activity grade I, available from M. Woelm, Eschwege, Germany, or from U.S. distributors.~~■1S (*USP27*)

Change to read:

[4] A suitable grade for the *Dissolution* test for Carisoprodol Tablets is Type VIII-A, from barley malt, available from ~~Sigma Chemical Company, St. Louis, MO 63178.~~

■Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[5] A suitable resin is "Amberlite IRA-400," ~~produced by Rohm and Haas Co., Philadelphia, PA 19105, and available through Mallinckrodt, Inc., P.O. Box 5439, St. Louis, MO 63147.~~

■available from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[6] A suitable resin is "AG-50W-X12," produced by BioRad Laboratories, ~~Attn: Chemical Division, 1000 Alfred Nobel Drive, Hercules, CA 94547.~~

■www.bio-rad.com.■1S (*USP27*)

Change to read:

[7] A suitable resin is "Dowex 1X4," ~~produced by the Dow Chemical Co., Midland, MI 48640, and available through J. T. Baker Chemical Co., Phillipsburg, NJ 08865.~~

■available from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[8] A suitable grade is available from ~~commercially from Eastman Kodak Co., Rochester, NY 14650.~~

■TCI America, www.tciamerica.com.■1S (*USP27*)

Change to read:

[9] A suitable grade is "Dioctyl Sebacate," ~~produced by the Harchem Division, Wallace and Tiernan, Inc., 25 Main St., Belleville, NJ 07101.~~

■available from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[10] A suitable grade is available from ~~Regis Chemical Co., 1101 N. Franklin St., Chicago, IL 60610.~~

■Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Delete the following:

■~~[11] A suitable grade is available from Aldrich Chemical Co., 940 W. St. Paul Ave., Milwaukee, WI 53233.~~ ■1S (*USP27*)

Delete the following:

■~~[12] Where Hammersten type casein is specified, a suitable grade is available commercially, as Catalog No. 7-E397, from J. T. Baker Chemical Co., 222 Red School Lane, Phillipsburg, NJ 08865.~~■1S (*USP27*)

Change to read:

[14] A suitable grade is available commercially as ~~"Dowex 50-W-X8, 20–50 Mesh" from J. T. Baker Chemical Co., Phillipsburg, NJ 08865.~~

■"Dowex 50-W- X8-100", from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[15] A suitable grade is available as "Bio-Rex 70" from BioRad Laboratories, ~~Attn: Chemical Division, 1000 Alfred Nobel Drive, Hercules, CA 94547.~~

■www.bio-rad.com.■1S (*USP27*)

Change to read:

[16] A suitable grade is available ~~commercially as ion exchange resin analytical grade, 50W-X2, 100–200 mesh, from BioRad Laboratories, Attn: Chemical Division, 1000 Alfred Nobel Drive, Hercules, CA 94547.~~

■as DOWEX-50X2-100, from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[17] A suitable resin is "Dowex 50W-X8," ~~produced by the Dow Chemical Co., Midland, MI 48640, and available through J.T. Baker Chemical Co., Phillipsburg, NJ 08865, or available in bulk form and in prefilled chromatography columns as "AG 50W-X8" from BioRad Laboratories, Attn: Chemical Division, 1000 Alfred Nobel Drive, Hercules, CA 94547.~~

■available from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[18] A suitable grade is available commercially as "Amberlyst 15" ~~from Rohm and Haas Co., Philadelphia, PA 19105, and from Mallinckrodt, Inc., Second and Mallinckrodt Sts., St. Louis, MO 63147, or as "Dowex 50-W-X2" from BioRad Laboratories, Attn: Chemical Division, 1000 Alfred Nobel Drive,Hercules, CA 94547.~~

■or as "Dowex 50-W-X2" from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[19] A suitable grade is available ~~as M-300 from Analtech, Inc., Newark, DE 19711.~~

■from EMD Chemicals, www.emdchemicals.com.■1S (*USP27*)

Change to read:

[20] A suitable grade is available commercially, in precoated plate form, ~~as "Eastman Chromagram Sheet Cellulose with fluorescent indicator," from Eastman Organic Chemicals, Rochester, NY 14650.~~

■with fluorescent indicator, from EMD Chemicals, www.emdchemicals.com.■1S (*USP27*)

Delete the following:

■~~[21] A suitable grade is available as "4-Chloroaniline", catalog number 47,722-2, from Sigma-Aldrich, Inc., P.O. Box 2060, Milwaukee, WI 53201.~~■1S (*USP27*)

Delete the following:

■~~[22] A suitable grade is available from Burdick and Jackson Laboratories, Inc., 1953 S. Harvey St., Muskegan, MI 49442.~~■1S (*USP27*)

Change to read:

[23] A suitable grade is available from GFS Chemicals, ~~Inc., 867 McKinley Ave., Columbus, OH 43223.~~

■www.gfschemicals.com.■1S (*USP27*)

Change to read:

[24] A suitable grade is "Chromosorb W, AW-DMCS," available from ~~Applied Science Laboratories, Inc., P.O. Box 440, State College, PA 16801.~~

■Alltech, www.alltechweb.com.■1S (*USP27*)

Change to read:

[26] Suitable grades are "Chromosorb P" and "Chromosorb W," available from ~~Johns Manville Corp., 22 East 40th St., New York, NY 10016.~~

■Alltech, www.alltechweb.com.■1S (*USP27*)

Change to read:

[27] A suitable grade is available

■as a mixture of the 2,7- and 2,8-isomers, catalog number ED-926,■1S (*USP27*)
from Cambridge Isotope Laboratories, Inc., ~~50 Frontage Road, Andover, MA 01810.~~

■www.isotope.com.■1S (*USP27*)

Change to read:

[28] A suitable grade is available from ~~Phase Separations, 140 Waters St., Norwalk, CT 06854.~~

■Alltech, www.alltechweb.com.■1S (*USP27*)

Change to read:

[30] A suitable grade is available as Ion Pair Cocktail Q12 (catalogue number 404031) from Regis Technologies, Inc., ~~8210 Austin Avenue, P.O. Box 519, Morton Grove, IL 60053; Web site:~~

■■1S (*USP27*)
www.registech.com.

Change to read:

[31] A suitable chromatographic grade is "Gas-Chrom Q," available from ~~Applied Science Laboratories, Inc., P.O. Box 440, State College, PA 16801.~~

■Alltech, www.alltechweb.com.■1S (*USP27*)

Delete the following:

■~~[32] Suitable grades are available commercially under the trade names "Florex XXS" (a moderately coarse powder) and "Florex XXX" (a very fine powder) from the Floridin Co., 3 Penn Center, Pittsburgh, PA 15235, or from laboratory supply houses.~~

~~NOTE—For the assay of Sorbitol and Sorbitol Solution, use a grade known as "Florex AARVM," available from the Floridin Co., or the equivalent.~~■1S (*USP27*)

Delete the following:

■[33] ~~A suitable grade is available from Boehringer Mannheim Biochemicals, P.O. Box 50414, Indianapolis, IN 46250.~~■1S (*USP27*)

Change to read:

[34] A suitable grade is available as Bovine Hemoglobin substrate powder from ~~Sigma Chemical Company, P.O. Box 14508, St. Louis, MO 63178-9916.~~

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■Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[35] Suitable grades are available commercially as Hexadecyl Palmitate, ~~Catalog number 940-419, from Phase Separations, 140 Waters St., Norwalk, CT 06854, Palmitic acid palmityl ester, Catalog number PO-169, from Sigma Chemical Company, P.O. Box 14508, St. Louis, MO 63178-9916, and Cetyl Palmitate, Catalog number C1203, from Spectrum Chemical Mfg. Corp., 14422 South San Pedro St., Gardena, CA 90248-9985.~~

■and Palmitic Acid Palmityl Ester from Sigma-Aldrich, www.sigma-aldrich.com and Cetyl Palmitate, Catalog number C1203, from Spectrum Chemical Mfg. Corp., www.spectrumchemical.com.■1S (*USP27*)

Delete the following:

■~~[36] A suitable grade is available from TCI America, 9211 N. Harborgate St., Portland, OR 97203.~~

Change to read:

[37] A suitable resin is ~~"Amberlite MB-1," produced by Rohm and Haas Co., Philadelphia, PA 19105.~~

■"Amberlite MB-150," available from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Delete the following:

■~~[38] A suitable grade is available as catalogue number 230139 from ICN Biomedicals, 1263 S. Chillicothe Road, Aurora, OH 44202.~~■1S (*USP27*)

Delete the following:

■~~[39] A suitable grade is available commercially from The Upjohn Co., Fine Chemicals Marketing, Kalamazoo, MI 49001.~~■1S (*USP27*)

Delete the following:

■~~[40] A suitable grade is available as Amadec F from Burdick and Jackson Laboratories, Inc., Muskegon, MI 49442.~~■1S (*USP27*)

Delete the following:

■~~[41] A suitable grade is "Florisil," available from the Floridin Co., 3 Penn Center, Pittsburgh, PA 15235.~~■1S (*USP27*)

Delete the following:

■~~[42] A suitable grade is "Florisil, 60–100 mesh," available from the Floridin Co., 3 Penn Center, Pittsburgh, PA 15235.~~■1S (*USP27*)

Change to read:

[44] A suitable grade is available as "2-naphthyl-6,8-disulfonic acid dipotassium salt" from Pfaltz and Bauer, Inc., ~~Div. of Aceto Chemical Corporation, 375 Fairfield Ave., Stamford, CT 06902.~~

■www.pfaltzandbauer.com.■1S (*USP27*)

Delete the following:

■~~[45] A suitable grade is available as Catalog No. C1115 from TCI America, 9211 N. Harborgate St., Portland, OR 97203.~~■1S (*USP27*)

Change to read:

[50] A suitable grade is available commercially as "Palladium Catalyst, Type I (5% Palladium on Calcium Carbonate)," from Engelhard Industries, Inc., ~~113 Astor St., Newark, NJ 07114.~~

■fax number (864) 885-1375.■1S (*USP27*)

Delete the following:

■~~[51] A suitable grade is available from Aldrich Library of Rare Chemicals, (CAS #103-81-1), 101 West Saint Paul Avenue, Milwaukee, WI 53233.~~■1S (*USP27*)

Delete the following:

■~~[52] A suitable grade is available from Aldrich Chemical Company, Inc., 1001 West Saint Paul Avenue, Milwaukee WI 53233, and Fluka Chemical Corp., 980 South 2nd Street, Ronkonkoma NY 11779-7238.~~■1S (*USP27*)

Change to read:

[53] A suitable grade is available from Worthington Biochemical Corp., ~~Route 9, Freehold, NJ 07728.~~

■www.worthington-biochem.com.■1S (*USP27*)

Change to read:

[54] A suitable grade is available commercially as "Brij-35". ~~from ICI Americas Inc., Wilmington, DE 19897.~~

■■1S (*USP27*)

Change to read:

[55] Suitable grades are available

■as catalog number U 232, ■1S (*USP27*)
from J. T. Baker Chemical Co., ~~Phillipsburg, NJ 08865 (Catalog No. U 232), or from E. I. du Pont de Nemours and Co., Wilmington, DE 19898 ("Elvanol 51-05").~~

■www.jtbaker.com.■1S (*USP27*)

Change to read:

[56] ~~Suitable grades are available as product numbers 33, 714-5, and~~

■A suitable grade is available as product number■1S (*USP27*) P4272 from Sigma-Aldrich, 1-800-558-9160; www.sigma-aldrich.com.

Change to read:

[57] A suitable grade is available commercially as "Silica Gel H". ~~from Brinkmann Instruments, Inc., Cantiague Rd., Westbury, NY 11590.~~

■■1S (*USP27*)

Change to read:

[58] ~~From H. J. Conn, "Biological Stains, 7th Edition," 1961, p. 294. Color Index No. 50240, Williams & Wilkins, Baltimore, MD.~~

■A suitable grade is available as catalog number 10, 214-8 from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[61] A suitable grade is available commercially as ''Silica Gel G''. ~~from Brinkmann Instruments, Inc., Cantiague Rd., Westbury, NY 11590.~~

■■1S (*USP27*)

Change to read:

[63] A suitable grade is available commercially as ''Silica Gel GF 254''. ~~from Brinkmann Instruments, Inc., Cantiague Rd., Westbury, NY 11590.~~

■■1S (*USP27*)

Change to read:

[64] A suitable grade is available as ''Silica Gel 60 silanized RP-2 F_{254},'' from ~~EM Industries, Inc., 7 Skyline Drive, Hawthorne, NY 10532.~~

■EMD Chemicals, www.emdchemicals.com.■1S (*USP27*)

Change to read:

[67] A suitable grade for reverse phase high-pressure liquid chromatography is available as ''LiChrosorb SI60, Reverse Phase''. ~~from EM SCIENCE, 480 Democrat Road, Gibbstown, NJ 08027.~~

■■1S (*USP27*)

Change to read:

[68] A suitable grade, in a controlled-diameter, spherical, porous form, is available commercially as ''Zorbax Sil,'' from ~~E. I. du Pont de Nemours and Co., Inc., Instrument Products Div., Wilmington, DE 19898.~~

■Agilent, www.agilent.com.■1S (*USP27*)

Change to read:

[69] A suitable grade is ''Chromosorb W-AW''. ~~available from Johns-Manville Corp., 22 East 40th St., New York, NY 10016.~~

■■1S (*USP27*)

Change to read:

[70] Suitable silanized grades for gas chromatography are ''Gas Chrom Q,'' ~~available from Applied Science Labs., Inc., P.O. Box 440, State College, PA 16801, and ''Chromosorb W (AW- DMCS-treated),'' available from Johns-Manville Corp., 22 East 40th Street, New York, NY 10016.~~

■and ''Chromosorb W (AW- DMCS-treated).■1S (*USP27*)

Change to read:

[71] A suitable grade for column chromatography is acid-washed ''Celite 545,'' available from ~~Johns Manville Corp., 22 East 40th St., New York, NY 10016.~~

■Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[73] A suitable grade is available as ''OV-25''. ~~from Applied Science Laboratories, Inc., P.O. Box 440, State College, PA 16801.~~

■■1S (*USP27*)

Delete the following:

■~~[74] A suitable grade is available from Research Plus Laboratories, Inc., Bayonne, NJ 07002.~~■1S (*USP27*)

Delete the following:

■~~[75] A suitable grade is ''No. 1252 Starch soluble GR meeting FIP standard,'' available from EM Science, 480 Democrat Road, Gibbstown, NJ 08027.~~■1S (*USP27*)

Change to read:

[77] A suitable grade is available commercially as ~~''BioBeads S-X3'' from Bio-Rad, Richmond, CA 94804.~~

■''BioBeads S-X'' from Bio-Rad, www.bio-rad.com.■1S (*USP27*)

Delete the following:

■~~[79] A suitable grade is available from Fisher Scientific Co., 711 Forbes Ave., Pittsburgh, PA 15215, and Burdick and Jackson Laboratories, Inc., Muskegon, MI 49442.~~■1S (*USP27*)

Delete the following:

■~~[80] A suitable preparation, listed as ''Freon TF aerosol,'' is available from E. I. du Pont de Nemours and Co., Wilmington, DE 19898~~■1S (*USP27*)

Change to read:

[82] A suitable grade is available as ''Meth-Prep II'' from Alltech, ~~Applied Science, P.O. Box 440, State College, PA 16801.~~

■www.alltechweb.com.■1S (*USP27*)

Delete the following:

■~~[84] A suitable grade is available from Fluka Chemical Corporation, 255 Oser Ave., Hauppause, NY 11788 and from Pfaltz and Bauer, Inc., Div. of Aceto Chemical Corporation, 375 Fairfield Ave., Stamford, CT 06902.~~■1S (*USP27*)

Change to read:

[85] A suitable grade is available, as a concentrate, from Worthington Diagnostics, Division of Millipore Corp., ~~Freehold, NJ 07728~~

■www.millipore.com.■1S (*USP27*)

Delete the following:

■~~[86] A suitable stock solution is available commercially as ''Topfer Reagent'' (0.5% methyl yellow in alcohol), from Anderson Laboratories, Inc., 5901 Fitzhugh Ave., P.O. Box 8429, Fort Worth, TX 76112.~~■1S (*USP27*)

Change to read:

[87] A suitable grade is available as ''Antifoam Reagent'', catalog number 2210, from Dow Corning Corporation, ~~Midland, MI 48686.~~

■www.dowcorning.com.■1S (*USP27*)

Delete the following:

■~~[88] A suitable grade is available from Fluka, 1-800-558-9160; Web site: www.sigma-aldrich.com.~~■1S (*USP27*)

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Change to read:

[89] A suitable grade is available as product number 5600 from Lancaster Synthesis, Inc., ~~P.O. Box 1000, Windham, NH 03087-9977.~~

■www.lancastersynthesis.com.■1S (*USP27*)

Change to read:

[90] A suitable grade is available as ~~"Human Total Protein" (8 g/dL), catalog number 540-10, from Sigma Chemical Co., St. Louis, MO 63178.~~

■Protein Standard Solution, catalog number 540-10, from Sigma-Aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Delete the following:

■~~[91] A suitable grade is available from Sigma-Aldrich, 1-800-558-9160; www.sigma-aldrich.com.~~■1S (*USP27*)

Delete the following:

■~~[92] A suitable grade is available from Sigma-Aldrich, 1-800-325-3010; www.sigma-aldrich.com.~~■1S (*USP27*)

Change to read:

[93] The reagent is available from Fluka Chemical Corporation, ~~1001 West St. Paul Avenue, Milwaukee, WI 53233.~~

■www.sigma-aldrich.com.■1S (*USP27*)

Change to read:

[95] A suitable grade is available as catalogue number M7,920-4 from ~~Aldrich Chemical Co., 940 W. St. Paul Ave., Milwaukee, WI 53233.~~

■Sigma-aldrich, www.sigma-aldrich.com.■1S (*USP27*)

Delete the following:

■~~[96] A suitable grade is available from Sigma-Aldrich, Inc., P.O. Box 2060, Milwaukee, WI 53201; www.sigma-aldrich.com~~■1S (*USP27*)

Add the following:

■[100]A suitable grade is available from either BD Biosciences, ~~Clontech, 1020 East Meadow Circle, Palo Alto, CA 94303-4230~~ www.bdbiosciences.com or Applied Biosystems, ~~850 Lincoln Centre Drive, Foster City, CA 94404.~~ www.appliedbiosystems.com.■1S (*USP27*)

Add the following:

■[101]A suitable grade is available from Applied Biosystems, ~~850 Lincoln Centre Drive, Foster City, CA 94404.~~ www.appliedbiosystems.com.■1S (*USP27*)

Add the following:

■[102]A suitable grade is available from BD Biosciences, ~~Clontech, 1020 East Meadow Circle, Palo Alto, CA 94303-4230.~~ www.bdbiosciences.com.■1S (*USP27*)

Add the following:

■[103]A suitable grade is commercially available as "Protex 6L" from Genencor, www.genencor.com~~200 Meridian Centre Blvd., Rochester, NY 14618,~~ or as "Optimase Enzyme" from Solvay Enzymes Inc., 1003 Industrial Pkwy, Elkhart, IN 46516. www.solvaypharmaceuticals.com.■1S (*USP27*)

Add the following:

■[105]A suitable grade is available as camphene, 95%, catalog number 45,606-5, from Sigma-Aldrich, ~~P.O. Box 2060, Milwaukee, WI 53201;~~ www.sigma-aldrich.com.■1S (*USP27*)

Add the following:

▲[106] Commercially available as DEAE-Sepharose.▲*USP27*

Add the following:

▲[107] There are many manufacturers and suppliers of these reagents that are licensed by the Center for Biological Evaluation and Research, Food and Drug Administration. Some examples of licensed manufacturers or suppliers are the following: Gamma Biologics, Houston, TX; and Ortho Diagnostics, Raritan, NJ.▲*USP27*

Add the following:

▲[109] The reagent is manufactured by Coulter Electronics Diagnostics, Hialeah, FL and is available from many suppliers under the name of Zapoglobin® (or Zapoglobin®).▲*USP27*

Add the following:

■[110] Available from Draeger Safety, Inc., www.draeger.com, or from Gastec Corp., www.gastec.co.jp, distributed in the USA by www.nextteq.com.■1S (*USP27*)

Add the following:

■[111] Available from Draeger Safety, Inc., www.draeger.com.■1S (*USP27*)

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 26* page 2540, page 3014 of the *First Supplement*, and page 508 of *PF* 29(2) [Mar.–Apr. 2003].

(HDQ) RTS—39761-2; 39894-2; 39894-3; 39894-5; 39894-6

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Add the following:	
▲Black Cohosh Tablets	T, LR▲*USP27*
Add the following:	
▲Desogestrel and Ethinyl Estradiol Tablets	W▲*USP27*
Add the following:	
■Irbesartan Tablets	W■1S (*USP27*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W■1S (*USP27*)
Add the following:	
■Isradipine Capsules	T■1S (*USP27*)
Add the following:	
■Loratadine Tablets	T■1S (*USP27*)
Add the following:	
■Quinapril Tablets	W■1S (*USP27*)

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 26* page 2546, page 3014 of the *First Supplement*, page 5310 of *PF* 23(6) [Nov.–Dec. 1997], page 7017 of *PF* 24(5) [Sept.–Oct. 1998], page 8282 of *PF* 25(3) [May–June 1999], page 8589 of *PF* 25(4) [July–Aug. 1999], page 8917 of *PF* 25(5) [Sept.–Oct. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 504 of *PF* 26(2) [Mar.–Apr. 2000], page 837 of *PF* 26(3) [May–June 2000], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1385 of *PF* 26(5) [Sept.–Oct. 2000], page 1907 of *PF* 27(1) [Jan.–Feb. 2001], page 2281 of *PF* 27(2) [Mar.–Apr. 2001], page 2839 of *PF* 27(4) [July–Aug. 2001], page 3120 of *PF* 27(5) [Sept.–Oct. 2001], page 3374 of *PF* 27(6) [Nov.–Dec. 2001], page 116 of *PF* 28(1) [Jan.–Feb. 2002], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 853 of *PF* 28(3) [May–June 2002], page 1236 of *PF* 28(4) [July–Aug. 2002], page1542 of *PF* 28(5) [Sept.–Oct. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], and page 509 of *PF* 29(2) [Mar.–Apr. 2003].

(HDQ) RTS—34173-1; 39490-1; 39490-2; 39520-1; 39536-3; 39536-5; 39566-1; 39703-1; 39704-1

Add the following:

■**Alfadex:** A white or almost white, amorphous or crystalline powder. Freely soluble in water and in propylene glycol; practically insoluble in ethanol and in methylene chloride.■1S (*USP27*)

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Add the following:

■**Betahistine Hydrochloride:** White to almost yellow, crystalline powder. Very hygroscopic. Melts between 151° and 154°. Very soluble in water; freely soluble in alcohol; practically insoluble in isopropyl alcohol.■1S (*USP27*)

Add the following:

■**Low-Substituted Carboxymethylcellulose Sodium:** A white or almost white powder or short fibers. Practically insoluble in acetone, in alcohol, and in toluene. It swells in water to form a gel.■1S (*USP27*)

Change to read:

Cefixime: White to light yellow, crystalline powder. ~~Freely soluble in methanol; soluble~~

■Soluble in methanol and■1S (*USP27*)
in propylene glycol; slightly soluble in alcohol, in acetone, and in glycerin; very slightly soluble in 70% sorbitol and in octanol; practically insoluble in ether, in ethyl acetate, in hexane, and in water.

Delete the following:

■~~**Cinoxate:** Slightly yellow, practically odorless, viscous liquid. Very slightly soluble in water; slightly soluble in glycerin; soluble in propylene glycol. Miscible with alcohol and with vegetable oils.~~■1S (*USP27*)

Add the following:

■**Cyclandelate:** White, crystalline powder. Very soluble in acetonitrile, in alcohol, and in ether; practically insoluble in water. Melts at about 58°.■1S (*USP27*)

Add the following:

■**Gemcitabine Hydrochloride:** White to off-white solid. Soluble in water; slightly soluble in methanol; practically insoluble in alcohol and in polar organic solvents.■1S (*USP27*)

Change to read:

~~**Hydroxypropyl Methylcellulose:**~~

■**Hypromellose:**■1S (*USP27*)
White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Change to read:

~~**Hydroxypropyl Methylcellulose 2208:**~~

■**Hypromellose 2208:**■1S (*USP27*)
White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Change to read:

~~**Hydroxypropyl Methylcellulose 2906:**~~

■**Hypromellose 2906:**■1S (*USP27*)
White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Change to read:

~~**Hydroxypropyl Methylcellulose 2910:**~~

■**Hypromellose 2910:**■1S (*USP27*)
White to slightly off-white, fibrous or granular powder. Swells in water and produces a clear to opalescent, viscous, colloidal mixture. Insoluble in dehydrated alcohol, in ether, and in chloroform. *NF category:* Coating agent; suspending and/or viscosity-increasing agent; tablet binder.

Add the following:

■**Hymetellose:** A white, yellowish-white or grayish-white powder or granules. Hygroscopic after drying. Dissolves in cold water, giving a colloidal solution; insoluble in hot water, in acetone, in alcohol, in ether, and in toluene.■1S (*USP27*)

Add the following:

■**Irbesartan:** White to off-white crystalline powder. Slightly soluble in alcohol and in methylene chloride; practically insoluble in water.■1S (*USP27*)

Add the following:

■**Loratadine:** White to off-white powder. Freely soluble in acetone, in chloroform, in methanol, and in toluene; insoluble in water.■1S (*USP27*)

Change to read:

Magnesium Oxide: Very bulky, white powder known as Light Magnesium Oxide or relatively dense, white powder known as Heavy Magnesium Oxide. ~~Five g of Light Magnesium Oxide occupies a volume of approximately 40 to 50 mL, while 5 g of Heavy Magnesium Oxide occupies a volume of approximately 10 to 20 mL.~~

■■1S (*USP27*)
Soluble in dilute acids; practically insoluble in water; insoluble in alcohol.

Delete the following:

■~~**Mandelic Acid:** White to yellowish white crystals or crystalline powder. Almost odorless. Gradually turns yellow and decomposes on prolonged exposure to light. Freely soluble in ether, in isopropyl alcohol, and in water; very soluble in alcohol; soluble in chloroform.~~■1S (*USP27*)

Add the following:

■**Nimodipine:** Light yellow or yellow, crystalline powder; affected by light. Freely soluble in ethyl acetate; sparingly soluble in alcohol; practically insoluble in water. Exhibits polymorphism.■1S (*USP27*)

Add the following:

■**Polyoxyl Lauryl Ether:** A material with 3–5 oxyethylene units per molecule is a colorless liquid. Soluble or dispersible in alcohol; practically insoluble in water and in hexane. A material with 9–23 oxyethylene units per molecule is a white, waxy mass. Soluble or dispersible in water; soluble in alcohol; practically insoluble in hexane. *NF category:* Emulsifying and/or solubilizing agent.■1S (*USP27*)

Add the following:

■**Polyoxyl Oleate:** A slightly yellowish, viscous liquid. Dispersible in water and in oils; soluble in alcohol and in isopropyl alcohol; miscible with fatty oils and with waxes. Its refractive index is about 1.466.■1S (*USP27*)

Add the following:

■**Polyoxyl Stearyl Ether:** A white to yellowish-white, waxy, unctuous mass, pellets, microbeads, or flakes. Polyoxyl Stearyl Ether with 2 oxyethylene units per molecule is practically insoluble in water; soluble in alcohol, with heating, and in methylene chloride. Polyoxyl Stearyl Ether with 10 oxyethylene units per molecule is soluble in water and in alcohol. Polyoxyl Stearyl Ether with 20 oxethylene units per molecule is soluble in water, in alcohol, and in methylene chloride. After melting, it solidifies at about 45°.■1S (*USP27*)

Add the following:

■**Quinapril Hydrochloride:** White to off-white powder, with a pink cast at times. Freely soluble in aqueous solvents.■1S (*USP27*)

Add the following:

■**Sodium Cetostearyl Sulfate:** A white or pale yellow, amorphous or crystalline powder. Soluble in hotwater giving an opalescent solution; partly soluble in alcohol; practically insoluble in cold water.■1S (*USP27*)

Add the following:

■~~**Stearoyl Macrogolglycerides:**~~ **Stearoyl Polyoxylglycerides:** Pale yellow, waxy solids. Dispersible in warm water and in warm paraffin; freely soluble in methylene chloride; soluble in warm methanol. *NF category:* Ointment base; solvent.■1S (*USP27*)

DIETARY SUPPLEMENTS–MONOGRAPHS

BRIEFING

Chaste Tree, page 139 of *PF* 28(1) [Jan.–Feb. 2002]; **Powdered Chaste Tree,** page 142 of *PF* 28(1) [Jan.–Feb. 2002]; **Powdered Chaste Tree Extract.** The first two monographs, which were previously presented in *Pharmacopeial Previews*, are now forwarded to *In-Process Revision*. The *Powdered Chaste Tree Extract* monograph is also proposed at this time using the methods and procedures for *Content of casticin* and *Content of agnuside* as directed in the *Chaste Tree* monograph.

(DSB: G. Giancaspro) RTS—35382-1

In-Process Revision

Add the following:

■Chaste Tree

» Chaste Tree consists of the dried ripe fruits of *Vitex agnus-castus* L. (Fam. Verbenaceae). It contains not less than 0.05 percent of agnuside and not less than 0.08 percent of casticin, calculated on the dried basis.

Packaging and storage—~~Store~~ Preserve in a well-closed ~~light-resistant~~ container, ~~protected from moisture~~and store at controlled room temperature.

Labeling—The label states the Latin binomial and, following the official name, the part of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Agnuside RS. USP Casticin RS. USP Powdered Chaste Tree Extract RS.*

Botanic characteristics—

Macroscopic—Mature chaste tree fruits are spherical to ovoid, 2 to 4 mm in diameter, very hard, usually with a short pedicil. The fruit is reddish brown to black, slightly rough, and covered with glandular hairs. There are four grooves perpendicular to one another, and a slight depression on the apex, more evident on large fruits. The internal appearance of the fruit is yellowish. The internal structure of the fruit includes four compartments, each containing an oblong seed with a high fat content. A group of up to six spongy, light tan, immature fruits also accompanies mature fruits. The fruit is often covered by a tubular, greenish gray, fine tomentous calyx, which is persistent and has five teeth.

Microscopic—The exocarp is brown and narrow, consisting of parenchymatous cells with thin walls and partially lignified cells with many pitted thickenings on the inside. In surface view, the exocarp shows an epidermis of polygonal cells with irregular thickenings and glandular hairs, each with a short single-celled stalk and a four-celled head containing essential oil. The outer mesocarp consists of several layers of brown, isodiametric parenchyma cells. The inner mesocarp consists of finely pitted sclerenchymatous cells, some with moderately thickened walls, others consisting of isodiametric stone cells with small lumen. The endocarp consists of a layer of small brown sclereid cells. The seeds are small, having large cotyledons surrounded by thin-walled large parenchymatous cells that have ribbed thickenings. The nutritive tissue and the cells of the germ contain aleuron grains and oil globules. Starch is absent. The outer epidermis of calyx is composed of polygonal cells, covered by abundant unicellular or multicellular curved trichomes. The inner epidermis of calyx is glabrous and composed of rectangular, elongated cells with slightly wavy walls.

Identification—

A: *Thin Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Transfer about 1 g of the powdered plant material to a screw-capped centrifuge tube. Add 10 mL of methanol, and heat in a water bath at 60° for 10 to15 minutes, cool, and filter. Apply 60 µL to the plate in bands that are 2 cm in length.

Standard solution—Transfer about 100 mg of USP Powdered Chaste Tree Extract RS to a screw-capped centrifuge tube. Add 1 mL of methanol, and heat in a water bath at 60° for 10 minutes. Centrifuge, and use the clear supernatant. Apply 20 to 30 µL to the plate.

Developing solvent system—Use the upper phase of a mixture of ethyl acetate, methanol, and water (77:15:8).

Spray reagent—Prepare a solution of *p*-dimethylaminobenzaldehyde in 1 N hydrochloric acid containing 10 mg per mL.

Procedure—Develop the chromatogram to a length of not less than 18 cm, and dry the plate in a current of air. Spray the plate with *Spray reagent*, and heat for 10 minutes at 120°. The chromatogram obtained from the *Test solution* shows the following: a blue zone (at an R_F value of about 0.21) that turns pink in time due to the presence of aucubin and that corresponds in color and R_F value to a similar zone in the chromatogram of the *Standard solution*; a blue zone (at an R_F value of about 0.44) that turns pink in time as a result of the presence of agnuside and that corresponds in color and R_F value to a similar zone in the chromatogram of the *Standard solution*; one yellow zone at an R_F value that is between that of agnuside and aucubin and corresponds in color and R_F value to a similar zone in the chromatogram of the *Standard solution*; and one yellowish-green zone (above a blue zone) that is near the solvent front and that corresponds in color and R_F value to a similar zone in the chromatogram of the *Standard solution.* Other colored zones of varying intensities may be observed in the chromatogram of the *Test solution.*

B: The chromatogram of the *Test solution* in the test for *Content of casticin* shows a peak at the retention time corresponding to the casticin peak in the chromatogram of the *Standard solution.*

Microbial limits ⟨2021⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.* The total aerobic microbial count does not exceed 10^6 per g, the total combined molds and yeast count does not exceed 10^4 per g, and the enterobacterial count does not exceed 10^3.

Loss on drying ⟨731⟩: not more than 10.0%.

Foreign organic matter ⟨561⟩: not more than 3.0%.

Total ash ⟨561⟩: not more than 8.0%.

Acid-insoluble ash ⟨561⟩: not more than 2.0%.

Pesticide residues ⟨561⟩: meets the requirements.

Heavy metals, *Method III* ⟨231⟩: not more than 20 µg per g.

Content of casticin—

Solution A—Use filtered and degassed methanol.

Solution B—Use a filtered and degassed solution of 5.88 g of phosphoric acid in 1000 mL of water.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Casticin RS in methanol, with sonication. Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.05 mg per mL. Filter through a cellulose membrane having a 0.45-µm or finer porosity.

Test solution—Accurately weigh approximately 1000 mg of ground plant material, and place in a suitable container with stopper. Extract twice with 40 mL of methanol, using a hand homogenizer at 19000 rpm for 2 minutes. Filter each supernatant, and transfer to a 250-mL round-bottom flask. Rinse the residue with methanol, and filter the resulting solution into the flask. Evaporate the combined extract to dryness. Dissolve the residue in methanol, quantitatively transfer to a 20-mL volumetric flask, and dilute with methanol to volume. Filter through a cellular membrane having a 0.45-µm or finer porosity.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 348-nm detector and a 3.1-mm × 12.5-cm column that contains 5-µm packing L1. The column temperature is maintained at 25°.

In-Process Revision

The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	50	50	Equilibration
0–13	50→65	50→35	Linear gradient
13–18	65→100	35→0	Linear gradient
18–23	100→50	0→50	Linear gradient

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor for casticin is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention time of the peak corresponding to casticin in the *Test solution* by comparison with the chromatogram of the *Standard solution.* Calculate the percentage of casticin in the portion of Chaste Tree taken by the formula:

$$2000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Casticin RS in the *Standard solution; W* is the weight, in mg, of the Chaste Tree taken to prepare the *Test solution;* and r_U and r_S are the peak responses of casticin obtained from the *Test solution* and the *Standard solution*, respectively.

Content of agnuside—

Solvent: a mixture of water and methanol (95:5).

Solution A—Use filtered and degassed acetonitrile.

Solution B—Use a filtered and degassed solution of 5.88 g of phosphoric acid in 1000 mL of water.

Standard solution—Dissolve an accurately weighed quantity of USP Agnuside RS in *Solvent*, with sonication. Dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.125 mg per mL. Filter through a cellulose membrane having a 0.45-µm or finer porosity.

Test solution—Accurately weigh approximately 1000 mg of ground plant material, and place in a suitable container with a stopper. Extract twice with 40 mL of methanol, using a hand homogenizer at 19000 rpm for 2 minutes. Centrifuge, and transfer each supernatant to a 250-mL round-bottom flask. Rinse the residue with methanol, and filter the resulting solution into the flask. Evaporate the combined extract to dryness, and dissolve the residue in 2 mL of *Solvent.* Quantitatively transfer the solution to a solid-phase extraction cartridge packed with neutral aluminum oxide previously conditioned with 5 mL of *Solvent.* Connect the cartridge to a vacuum pressure not exceeding 300 mbar, and collect the eluate. Rinse the round-bottom flask with 2 mL of *Solvent*, and pass this solution through the cartridge, apply the vacuum, and collect the eluate. Rinse the cartridge with 4 mL of *Solvent*, and collect the eluate. Combine the eluates from the cartridge, transfer to a 10-mL volumetric flask, and dilute with *Solvent* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 258-nm detector and a 3.1-mm × 12.5-cm column that contains 5-µm packing L1. The column temperature is maintained at 25°.

The flow rate is about 1.3 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	7	93	Equilibration
0–0.6	7→10	93→90	Linear gradient
0.6–5	10	90	Isocratic
5–7	10→14	90→86	Linear gradient
7–13	14→15	86→85	Linear gradient
13–13.1	15→100	85→0	Linear gradient
13.1–18	100	0	Isocratic
18–18.1	100→7	0→93	Linear gradient
18.1–23	7	93	Re-equilibration

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor for agnuside is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Identify the retention time of the peak corresponding to agnuside in the the *Test solution* by comparison with the chromatogram obtained from the *Standard solution.* Calculate the percentage of agnuside in the portion of Chaste Tree taken by the formula:

$$1000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Agnuside RS in the *Standard solution; W* is the weight, in mg, of the Chaste Tree taken to prepare the *Test solution;* and r_U and r_S are the peak responses of agnuside obtained from the *Test solution* and the *Standard solution*, respectively.■1S (*USP27*)

BRIEFING

Powdered Chaste Tree, page 142 of *PF* 28(1) [Jan.–Feb. 2002]—See briefing under *Chaste Tree.*

(DSB: G. Giancaspro) RTS—35382-2

Add the following:

■Powdered Chaste Tree

» Powdered Chaste Tree is Chaste Tree reduced to a powder or a very fine powder. It contains not less than 0.05 percent of agnuside and not less than 0.08 percent of casticin, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

Labeling—The label states the Latin binomial and, following the official name, the part of the plant from which the article was derived.

USP Reference standards ⟨11⟩—*USP Agnuside RS. USP Casticin RS. USP Powdered Chaste Tree Extract RS.*

Botanic characteristics—Powdered Chaste Tree is dark brown, with a musty, slightly aromatic odor, and a taste resembling that of sage. The following characteristics are present: fragments of the calyx with covering and glandular trichomes on the outer side and rectangular, elongated cells with slightly wavy walls on the inner side; fragments of exocarp with trichomes and cells with large pits in the outer wall; thin-walled parenchymatous cells and globules of fixed oil; stone-pitted cells from the mesocarp; ovoid, lignified cells with bands of reticulate thickening from the testa; and endosperm and cotyledons with fixed oil.

In-Process Revision

Other requirements—It meets the requirements of the tests for *Identification*, *Microbial limits*, *Loss on drying*, *Total ash*, *Acid-insoluble ash*, *Pesticide residues*, *Heavy metals*, *Content of casticin*, and *Content of agnuside* under *Chaste Tree*.■ IS (*USP27*)

BRIEFING

Powdered Chaste Tree Extract. Because there is no existing monograph for this article, this new monograph is being proposed. See also the briefing under *Chaste Tree*.

(DSB: G. Giancaspro) RTS—39958-1

Add the following:

■Powdered Chaste Tree Extract

» Powdered Chaste Tree Extract is prepared from Chaste Tree by extraction with hydroalcoholic mixtures or other suitable solvents. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of casticin and agnuside, calculated on the dried basis. It may contain suitable added substances.

Packaging and storage—Preserve in tight containers, and store in a cool place, protected from light.

Labeling—The label states the Latin binomial and, following the official name, the part of the plant from which the article was prepared. The label also indicates the content of casticin and agnuside, the extracting solvent or solvent mixture used for preparation, the ratio of the starting crude plant material to Powdered Extract, the percentage of native extract, and the name and quantity of any added substances. It meets the requirements for *Labeling* under *Botanical Extracts* ⟨565⟩.

USP Reference standards ⟨11⟩—*USP Agnuside RS. USP Casticin RS. USP Powdered Chaste Tree Extract RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent, *Standard solution*, *Developing solvent system*, and *Procedure*—Proceed as directed for *Identification* in *Chaste Tree*.

Test solution—Shake the amount of Extract equivalent to 10 mg of the labeled amount of agnuside in 10 mL of methanol, and heat in a water bath at 60°. Centrifuge or filter before use.

B: The chromatogram of the *Test solution* obtained as directed in the *Content of casticin*, exhibits a peak at the retention time corresponding to casticin.

C: The chromatogram of the *Test solution* obtained as directed in the *Content of agnuside*, exhibits a peak at the retention time corresponding to agnuside.

Loss on drying ⟨731⟩: not more than 6.0%.

Heavy metals, *Method II* ⟨231⟩: not more than 20 µg per g.

Organic volatile impurities, *Method VI* ⟨467⟩: meet the requirements.

Microbial limits ⟨2021⟩—The total bacterial count does not exceed 10^4 per g. The total combined molds and yeasts count does not exceed 10^3 per g. It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

Content of casticin—

Solution A, *Solution B*, *Standard solution*, and *Chromatographic system*—Proceed as directed under *Chaste Tree*.

Test solution—Transfer an accurately weighed amount of Extract equivalent to about 2.5 mg of labeled content of casticin into a 50-mL volumetric flask. Add 25 mL of methanol, and sonicate in a bath at 40° for 10 minutes shaking to disperse the solid. Cool to room temperature, and dilute with methanol to volume, and mix. Centrifuge or pass through a filter having a 0.45-µm or finer porosity.

Procedure—Proceed as directed for *Procedure* under *Chaste Tree*. Calculate the percentage of casticin in the portion of Powdered Chaste Tree Extract taken by the formula:

$$5000(C/W)(r_U/r_S),$$

in which, the terms are defined therein.

Content of agnuside—

Solvent, *Solution A*, *Solution B*, *Standard solution*, and *Chromatographic system*—Proceed as directed under *Chaste Tree*.

Test solution—Transfer an accurately weighed amount of Extract equivalent to about 6.25 mg of labeled content of agnuside into a 50-mL volumetric flask. Add about 25 mL of *Solvent* and sonicate a bath at 40° for 10 minutes shaking to disperse the solid. Cool to room temperature and dilute to volume with *Solvent* and mix. Centrifuge or pass through a filter having a 0.45-µm or finer porosity.

Procedure—Proceed as directed for *Procedure* under *Chaste Tree*. Calculate the percentage of agnuside in the portion of Powdered Chaste Tree Extract taken by the formula:

$$5000(C/W)(r_U/r_S),$$

in which, the terms are as defined therein.

Other requirements—It meets the requirements for *Packaging and Storage*, *Residual Solvents*, and *Pesticide Residues* under *Botanical Extracts* ⟨565⟩.■1S (*USP27*)

BRIEFING

Chondroitin Sulfate Sodium, *NF 21* page 2721, page 3018 of the *First Supplement*, and page 456 of *PF* 29(2) [Mar.–Apr. 2003]. Significant differences between chondroitin of fish origin and the type of chondroitin described by this monograph are found in the IR spectra between 1000 cm^{-1} and 450 cm^{-1}. No significant difference is observed between chondroitin from avian, porcine, and bovine origins in this region. Therefore, it is proposed to remove the limitation in the spectral range under *Identification* test *A*. In the test for *Residue on ignition*, it is proposed not to omit the addition of sulfuric acid. Having removed the proposed requirement to detect sulfate ions as obtained in the *Residue on ignition* test (see pages 3059–3063 of *PF* 27(5) [Sept.–Oct. 2001]) from the *Identification* tests in the monograph, the omission of sulfuric acid is no longer necessary. It is reported that more consistent results are obtained when sulfuric acid is added to char the test specimen as directed in the general chapter *Residue on Ignition* ⟨281⟩.

(DSB: G. Giancaspro) RTS—39813-1

Change to read:

~~(Chemical structure to come)~~

~~$(C_{14}H_{20}NO_{14}SNa_2)_n$~~
~~Sodium chondroitin sulfate~~ ~~[24967-93-9]~~

▲Chondroitin, hydrogen sulfate, sodium salt [*9082-07-9*]▲*USP27*

Change to read:

» Chondroitin Sulfate Sodium is the sodium salt of the sulfated linear glycosaminoglycan obtained from bovine, porcine, or avian cartilages of healthy and domestic animals used for food by humans. Chondroitin Sulfate Sodium consists mostly of the sodium salt of the sulfate ester of *N*-acetylchondrosamine (2-acetamido-2-deoxy-β-D-galactopyranose) and D-glucuronic acid copolymer. These hexoses are alternately linked β-1,4 and β-1,3 in the polymer. ~~The prevalent glycosaminoglycans are designated chondroitin sulfate sodium A, containing *N*-acetylchondrosamine-4-*O*-sulfate, and chondroitin sulfate sodium C, containing *N*-acetylchondrosamine-6-*O*-sulfate.~~

▲Chondrosamine moieties in the prevalent glycosaminoglycan are monosulfated primarily on position 4 and less so on position 6.▲*USP27*

It contains not less than 90.0 percent and not more than 105.0 percent of ~~total glycosaminoglycans as~~

In-Process Revision

▲*USP27*
chondroitin sulfate sodium, calculated on the dried basis.

NOTE—Chondroitin Sulfate Sodium is extremely hygroscopic once dried. Avoid exposure to the atmosphere and weigh promptly.

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩. ~~Proceed as directed in the chapter, except to record the spectrum from 3800 to 1000 cm⁻¹.~~

■■1S (*USP27*)
B: A solution containing 0.5 g in 10 mL of water meets the requirements of the test for *Sodium* ⟨191⟩.

Change to read:

■**Test for absence of *clostridium* species—**

Test preparation—Provide separate 10-g specimens for each of the tests called for below. Dissolve Chondroitin Sulfate Sodium in *pH 7.2 Phosphate buffer.* [NOTE—On the basis of results for *Preparatory testing*, modify the *Test preparation* as appropriate.]

Preparatory testing—Incubate *Clostridium sporogenes* (ATCC No. 11437) for 18 to 24 hours, and then dilute with *pH 7.2 Phosphate buffer.* Inoculate the *Test preparation*, to obtain a final concentration of less than 100 cfu per mL. Controls containing the inoculum but without the material under test are prepared at the same time. Proceed as directed under ~~*Test for absence of clostridium species,*~~

▲*Procedure,* ▲*USP27*
making sure to evaluate the growth after each time a medium is added.

Results—Proceed as directed for *Preparatory Testing* under *Microbial Limit Tests—Nutritional Supplements* ⟨2021⟩.

REINFORCED MEDIUM FOR CLOSTRIDIA

Beef Extract	10.0 g
Peptone	10.0 g
Yeast Extract	3.0 g
Soluble Starch	1.0 g
Glucose Monohydrate	5.0 g
Cysteine Hydrochloride	0.5 g
Sodium Chloride	5.0 g
Sodium Acetate	3.0 g
Agar	0.5 g
Water	1000 mL

Dissolve agar in water by heating to boiling, while stirring continuously. Adjust the pH if necessary, and sterilize.

pH after sterilization: 6.8 ± 0.2.

COLUMBIA AGAR

Pancreatic Digest of Casein	10.0 g
Meat Peptic digest	5.0 g
Heart Pancreatic digest	3.0 g
Yeast Extract	5.0 g
Corn Starch	1.0 g
Sodium Chloride	5.0 g
Agar	15.0 g
Water	1000 mL

Dissolve agar in water by heating to boiling with continuous stirring. If necessary, adjust the pH. Sterilize, and allow to cool to 45° to 50°. Add gentamicin sulfate, equivalent to about 20 mg of gentamicin base, and pour into Petri dishes.

pH after sterilization: 7.3 ± 0.2.

Procedure—Take two equal portions of the *Test preparation*, heat one to 80° for 10 minutes, and cool rapidly. Transfer 10 mL of each portion to separate containers, each containing each 100 mL of *Reinforced Medium for Clostridia*, and incubate under anaerobic conditions at 35° to 37° for 48 hours. After incubation subculture each specimen on *Columbia Agar Medium* to which gentamicin has been added, and incubate under anaerobic conditions at 35° to 37° for 48 hours. Examine the plates, and interpret as follows: if no growth of Gram-positive rods is detected, the test specimen meets the requirement for the absence of *Clostridium* species.

If growth occurs, subculture each distinct colony on *Columbia Agar Medium*, and separately incubate in aerobic and in anaerobic conditions at 35° to 37° for 48 hours. The occurrence of only anaerobic growth of Gram-positive bacilli, giving a negative catalase reaction, indicates the presence of *Clostridium sporogenes* species. To perform the catalase test, transfer discrete colonies to glass slides, and apply a drop of dilute hydrogen peroxide solution: the reaction is negative if no gas bubbles evolve. If the test specimen exhibits none of these characteristics, it meets the requirement for the absence of *Clostridium* species.■1S (*NF21*)

Change to read:

Residue on ignition ⟨281⟩: between 20.0% and 30.0%, on the dried basis. ~~, omitting the addition of sulfuric acid.~~

■■1S (*USP27*)

Change to read:

Limit of protein—

▲*Alkaline cupric tartaric reagent*—Dissolve 200 mg of sodium tartrate dihydrate in 10 mL of water, and mark as *Solution A* . Dissolve 100 mg of cupric sulfate in 10 mL of water, and mark as *Solution B*. Dissolve 2.0 g of anhydrous sodium carbonate in 0.1 M sodium hydroxide, dilute with 0.1 M sodium hydroxide, to 100 mL and mark as *Solution C*. Mix well 1 mL of *Solution A* and 1 mL of *Solution B*, and to the mixture slowly add 100 mL of *Solution C* with stirring. Use within 24 hours, and discard afterwards.▲*USP27*

Standard solution—Transfer an accurately measured volume of 7 percent bovine serum albumin certified standard to a suitable container, and dilute quantitatively and stepwise with water to obtain a solution having a known concentration of about 35 µg per mL.

Test solution—Transfer an accurately weighed amount of Chondroitin Sulfate Sodium, equivalent to ■60 mg■1S (*NF21*) of the dried substance, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Procedure—Add 2.0 mL of freshly prepared ~~alkaline cupric tartrate TS~~

▲*Alkaline cupric tartaric reagent*▲*USP27*
to test tubes containing 2.0 mL of water, 2.0 mL of the *Test solution*, or 2.0 mL of the *Standard solution*, and mix. After about 10 minutes, add 1.0 mL of Folin-Ciocalteu phenol TS, prepared immediately before use, to each test tube, and mix. After 30 minutes, measure the absorbance of each solution at 750 nm against the blank. The absorbance of the *Test solution* is not greater than the absorbance of the *Standard solution:* not more than ■6.0%■1S (*NF21*) of proteins is found, calculated on the dried basis.

Change to read:

Content of ~~total glycosaminoglycans~~

▲chondroitin sulfate sodium▲*USP27*

—Cetylpyridinium chloride solution—Prepare a solution of cetylpyridinium chloride in water having a concentration of about 1 mg per mL.

Standard ■*solutions*■1S (*NF21*)—Transfer about ■30 mg■1S (*NF21*) of USP Chondroitin Sulfate Sodium RS, accurately weighed, to a 25-mL volumetric flask. Dissolve in 6 mL of water, add 1 mL of pH 7.2 phosphate buffer solution (see *Buffer Solutions* under *Solutions* in the section *Reagents*, *Indicators*, *and Solutions*), and dilute with water■, quantitatively and stepwise if necessary,■1S (*NF21*) to obtain ■three *Standard solutions*■1S (*NF21*) having known concentrations of about ■1.2 mg per mL, 0.8 mg per mL, and 0.4 mg per mL, respectively.■1S (*NF21*)

Test solution—Transfer about 100 mg of dried Chondroitin Sulfate Sodium, accurately weighed, to a 100-mL volumetric flask, dissolve in 30 mL of water, add 5 mL of pH 7.2 phosphate buffer solution (see *Buffer Solutions* under *Solutions* in the section *Reagents*, *Indicators*, *and Solutions*), dilute with water to volume, and mix.

Procedure—Transfer 5.0 mL of ■each■1S (*NF21*) *Standard solution* ■and the *Test solution* to four separate titration vessels,■1S (*NF21*) and add about 30 mL of water. ■Stir until a steady reading is obtained using a phototrode to determine the endpoint turbidimetrically, either at 420 nm, 550 nm, or 660 nm. Set the instrument to zero if absorbance is being monitored or not less than 70% if transmittance is used. Titrate with *Cetylpyridinium chloride solution*. From a linear regression equation calculated using the volumes of *Cetylpyridinium chloride solution* consumed, and the mass, in mg, of USP Chondroitin Sulfate Sodium RS, determine the mass of ~~glycosaminoglycans as~~ ▲*USP27* chondroitin sulfate sodium in the aliquot of the *Test solution* taken.■1S (*NF21*) Calculate the percentage of ~~total mucopolysaccharides glycosaminoglycans as~~ ▲*USP27* chondroitin sulfate sodium in the portion ~~of Chondroitin Sulfate Sodium~~ ▲*USP27* taken by the formula:

$$■2000(M/W),■1S\ (NF21)$$

in which ■*M* is the mass of ~~glycosaminoglycans~~ ▲Chondroitin Sulfate Sodium▲*USP27* in the aliquot of the *Test solution*,■1S (*NF21*) and *W* is the weight, in mg, of Chondroitin Sulfate Sodium taken to prepare the *Test solution*.

BRIEFING

Fish Oil Rich in Omega-3 Acids. Because there is no existing *USP* or *NF* monograph for this article, this new monograph is being proposed. The chromatographic procedure was validated using a Supelcowax-10 brand of capillary column G16. Typical retention times are 19.4 minutes for eicosapentaenoic acid (EPA) methyl ester, 24.2 minutes for methyl tricosanoate, and 28.8 minutes for docosahexaenoic acid (DHA) methyl ester. Oxidation indexes and limits for heavy metals and pesticides are based on the Council for Responsible Nutrition's voluntary monograph for omega-3 acids.

(DSN: G. Giancaspro) RTS—39705-1

Add the following:

■Fish Oil Rich in Omega-3 Acids

» Fish Oil Rich in Omega-3 Acids is the purified, winterized, and deodorized fatty oil obtained from fish of the families *Engraulidae*, *Carangidae*, *Clupeidae*, *Osmeridae*, *Scrombroidae*, and *Ammodytidae*. The omega-3 acids are defined as the following: alpha-linolenic acid (C18:3 n-3), moroctic acid (C18:4 n-3), eicosatetraenoic acid (C20:4 n-3), eicosapentaenoic acid (EPA) (C20:5 n-3), heneicosapentaenoic acid (C21:5 n-3), docosapentaenoic acid (C22:5 n-3), and docosahexaenoic acid (DHA) (C22:6 n-3). It contains not less than 28.0 percent of total omega-3 acids, expressed as triglycerides, consisting of not less than 13.0 percent of EPA and not less than 9.0 percent of DHA. Suitable antioxidants in appropriate concentrations may be added.

Packaging and storage—Preserve in tight, light-resistant containers at controlled room temperature. It may be bottled or otherwise packaged in containers from which air has been expelled by production of vacuum or by an inert gas.

Labeling—The label states the average content of DHA and EPA in mg per g. It also states the name and concentration of any added antioxidant.

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USP Reference standards ⟨11⟩—*USP Cod Liver Oil RS*. *USP Methyl Tricosanoate RS*.

Identification—The retention times of the peaks for eicosapentaenoic acid methyl ester and docosahexaenoic acid methyl ester obtained in the chromatogram of the *Test solutions* in the test for *Content of EPA and DHA* correspond to those for the respective compounds in the chromatogram of the *Standard solution*. The sum of the area for EPA and DHA methyl esters is not less than 28% of the total detected area for the methyl esters, and no other peak in the chromatogram has an area higher than 20% of the total detected area for the methyl esters. The chromatogram of *Test solution 1* exhibits at least 15 additional peaks at the retention times of the methyl esters of unsaturated fatty acids exhibited in the chromatogram of the *Standard solution.*

Acid value ⟨401⟩—Not more than 3.

Anisidine value ⟨401⟩—Not more than 20.0.

Peroxide value ⟨401⟩—Not more than 5.0.

Total oxidation value (TOTOX) ⟨401⟩—Not more than 26, calculated by the formula:

$$(2 \times PV) + AV,$$

in which *PV* is the *Peroxide value*, and *AV* is the *Anisidine value*.

Unsaponifiable matter ⟨401⟩—Not more than 1.5 percent.

Stearin—100 mL remains clear after cooling at 0° for 3 hours.

Absorbance—Not more than 0.70, determined at 233 nm.

Limit of arsenic—[NOTE—For the preparation of all aqueous solutions and for the rinsing of glass, polytef, and plastic vessels before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of arsenic as practicable, and store all reagent solutions in containers of borosilicate glass. Cleanse glass, polytef, and plastic vessels before use by soaking in warm 8 N nitric acid for 30 minutes and by rinsing with deionized water.]

Standard stock solution—Transfer 10.0 mL of *Standard Arsenic Solution*, prepared as directed in the test for *Arsenic* ⟨221⟩, to a 100-mL volumetric flask, add 40 mL of water and 5 mL of nitric acid, dilute with water to volume, and mix. This solution contains 0.10 µg of arsenic per mL.

Standard solutions—Dilute the *Standard stock solution* with *Blank* to obtain solutions containing, respectively, 0.002, 0.005, 0.010, 0.025 and 0.050 µg per mL, of Arsenic.

Test solution—For preparation of the *Test solution*, use a microwave oven with a magnetron frequency of about 2455 MHz and a selectable output power of 0 to 950 watts in 1% increments, equipped with advanced composite vessels with 100-mL polytef liners. Use rupture membranes to vent vessels should the pressure exceed 125 psi. The vessels fit into a turntable, and each vessel can be vented into an overflow container. Equip the microwave oven with an exhaust tube to ventilate fumes. [*Caution—Wear proper eye protection and protective clothing and gloves.*] Transfer approximately 500 mg of sample, accurately weighed to the nearest 0.1 mg, into a Teflon digestion vessel liner. Prepare samples in duplicate. Add 15 mL of nitric acid, and swirl gently. Cover the vessels with lids, leaving the vent fitting off. Predigest overnight under a hood. Place the rupture membrane in the vent fitting, and tighten the lid. Place all vessels on the microwave oven turntable. Connect the vent tubes to the vent trap, and connect the pressure-sensing line to the appropriate vessel. Initiate a two-stage digestion procedure by heating the microwave at 15% power for 15 minutes followed by 25% power for 45 minutes. Remove the turntable of vessels from the oven, and allow the vessels to cool to room temperature (a cool water bath may be used to speed the cooling process). Vent the vessels when they reach room

temperature. Remove the lids, and slowly add 2 mL of 30% hydrogen peroxide to each. Allow the reactions to subside, and seal the vessels. Return the vessels on the turntable to the microwave oven, and heat for an additional 15 minutes at 30% power. Remove the vessels from the oven, and allow them to cool to room temperature. Transfer the cooled digests into 25-mL volumetric flasks, and dilute with water to volume.

Blank—Transfer 5 mL of nitric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

1% Palladium stock solution—Transfer 1 g of ultrapure palladium metal, accurately weighed, into a Teflon beaker. Add 20 mL of water and 10 mL of nitric acid, and warm on a hot plate to dissolve. Allow the solution to cool to room temperature, transfer it into a 100-mL volumetric flask, and dilute with deionized water to volume.

1% Magnesium nitrate stock solution—Transfer 1 g of ultrapure magnesium nitrate, accurately weighed, into a Teflon beaker. Add 40 mL of water and 1 mL of nitric acid, and warm on a hot plate to dissolve the solids. Allow the solution to cool to room temperature, transfer it into a 100-mL volumetric flask, and dilute with deionized water to volume.

Modifier working solution—Transfer 3 mL of *1% Palladium stock solution* and 2 mL of *1% Magnesium nitrate stock solution* into a 10-mL volumetric flask, and dilute with 2% nitric acid to volume. A volume of 5 µL provides 0.015 mg of palladium and 0.01 mg of magnesium nitrate.

Procedure—Program the graphite furnace as follows: (1) dry at 115° using a 1-second ramp, a 65-second hold, and a 300 mL per minute argon flow; (2) char the sample at 1000° using a 1-second ramp, a 20-second hold, and a 300 mL per minute air flow; (3) cool down, and purge the air from the furnace for 10 seconds using a 20° set temperature and a 300 mL per minute argon flow; (4) atomize at 2400° using a 0-second ramp and a 5-second hold with the argon flow stopped; and (5) clean out at 2600° with a 1-second ramp and a 5-second hold. Separately inject equal volumes (about 20 µL) of the *Test solutions* and the *Blank*, and 5 µL of the modifier solution, into the graphite tube of a suitable graphite furnace atomic absorption spectrophotometer equipped with a hollow cathode lamp for arsenic. Determine the peak area at the arsenic emission line at 193.7 nm, corrected for background absorption. Plot the corrected peak areas of the *Standard solutions* versus their contents of arsenic, in µg per mL, and calculate the regression line best fitting the points. Determine the concentration, C, in µg per mL, of arsenic in each mL of the test solution by interpolation from the regression line. Calculate the content of arsenic in the specimen taken by the formula:

$$25\ C/W,$$

in which W is the weight, in g, of Fish Oil taken to prepare the *Test solution:* not more than 0.1 µg per g is found.

Limit of lead—[NOTE—For the preparation of all aqueous solutions and for the rinsing of glass, polytef, and plastic vessels before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of lead as practicable, and store all reagent solutions in containers of borosilicate glass. Cleanse glass, polytef, and plastic vessels before use by soaking in warm 8 N nitric acid for 30 minutes and by rinsing with deionized water.]

10% Ammonium dihydrogen phosphate stock solution—Transfer 10 g of ultrapure ammonium dihydrogen phosphate, accurately weighed, into a 100-mL volumetric flask. Add 40 mL of water and 1 mL of nitric acid to dissolve the phosphate. Dilute with deionized water to 100 mL.

1% Magnesium nitrate stock solution—Transfer 1 g of ultrapure magnesium nitrate, accurately weighed, into a Teflon beaker. Add 40 mL of water and 1 mL of nitric acid,

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and warm on a hot plate to dissolve the solids. Allow the solution to cool to room temperature, transfer it into a 100-mL volumetric flask, and dilute with deionized water to volume.

Modifier working solution—Transfer 4 mL of *10% Ammonium dihydrogen phosphate stock solution* and 2 mL of *1% Magnesium nitrate stock solution* into a 10-mL volumetric flask, and dilute with 2% nitric acid to volume. A volume of 5 µL provides 0.2 mg of phosphate plus 0.01 mg of magnesium nitrate.

Standard stock solution—Transfer 10.0 mL of *Lead Nitrate Stock Solution*, prepared as directed in the test for *Heavy Metals* ⟨231⟩, to a 100-mL volumetric flask, add 40 mL of water and 5 mL of nitric acid, dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a second 100-mL volumetric flask, add 50 mL of water and 1 mL of nitric acid, dilute with water to volume, and mix. This solution contains 0.10 µg of lead per mL.

Test solution—Prepare as directed for *Test solution* in the test for *Limit of arsenic*.

Blank—Transfer 5 mL of nitric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solutions—Dilute the *Standard stock solution* with *Blank* to obtain solutions containing, respectively, 0.002, 0.005, 0.010, 0.025, and 0.050 µg per mL of lead.

Procedure—Program the graphite furnace as follows: (1) dry at 120° using a 1-second ramp, a 55-second hold, and a 300 mL per minute argon flow; (2) char the sample at 850° using a 1-second ramp, a 30-second hold, and a 300 mL per minute air flow; (3) cool down, and purge the air from the furnace for 10 seconds using a 20° set temperature and a 300 mL per minute argon flow; (4) atomize at 2100° using a 0-second ramp and a 5-second hold with the argon flow stopped; and (5) clean out at 2600° with a 1-second ramp and a 5-second hold. Separately inject equal volumes (about 20 µL) of the *Test solutions* and the *Blank*, and 5 µL of the *Modifier working solution*, into the graphite tube of a suitable graphite furnace atomic absorption spectrophotometer equipped with a hollow cathode lamp for lead. Determine the peak area at the lead emission line at 283.3 nm, corrected for background absorption. Plot the corrected peak areas of the *Standard solutions* versus their contents of lead, in µg per mL, and calculate the regression line best fitting the points. Determine the concentration, C, in µg per mL, of lead in each mL of the *Test solution* by interpolation from the regression line. Calculate the content of lead in the specimen taken by the formula:

$$25\ C/W,$$

in which W is the weight, in g, of Fish Oil taken to prepare the *Test solution:* not more than 0.1 µg per g is found.

Limit of cadmium—[NOTE—For the preparation of all aqueous solutions and for the rinsing of glass, polytef, and plastic vessels before use, employ water that has been passed through a strong-acid, strong-base, mixed-bed ion-exchange resin before use. Select all reagents to have as low a content of cadmium as practicable, and store all reagent solutions in containers of borosilicate glass. Cleanse glass, polytef, and plastic vessels before use by soaking in warm 8 N nitric acid for 30 minutes and by rinsing with deionized water.]

10% Ammonium dihydrogenphosphate stock solution—Transfer 10 g of ultrapure ammonium dihydrogen phosphate, accurately weighed, into a 100-mL volumetric flask. Add 40 mL of water and 1 mL of nitric acid to dissolve the phosphate. Dilute to 100 mL with deionized water.

1% Magnesium nitrate stock solution—Transfer 1 g of ultrapure magnesium nitrate, accurately weighed, into a teflon beaker. Add 40 mL of water and 1 mL of nitric acid, and

warm on a hot plate to dissolve the solids. Allow the solution to cool to room temperature, transfer it into a 100-mL volumetric flask, and dilute with deionized water to volume.

Modifier working solution—Transfer 4 mL of *10% Ammonium dihydrogen phosphate stock solution* and 2 mL of *1% Magnesium nitrate stock solution* into a 10-mL volumetric flask, and dilute with 2% nitric acid to volume. A volume of 5 µL provides 0.2 mg of phosphate plus 0.01 mg of magnesium nitrate.

Standard stock solution—Transfer 137.2 mg of cadmium nitrate to a 1000-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a second 100-mL volumetric flask, add 50 mL of water and 1 mL of nitric acid, dilute with water to volume, and mix. This solution contains 0.10 µg of cadmium per mL.

Test solution—Prepare as directed for *Test solution* in the test for *Limit of arsenic*.

Blank—Transfer 5 mL of nitric acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solutions—Dilute the *Standard stock solution* with *Blank* to obtain solutions containing, respectively, 0.002, 0.005, 0.010, 0.025, and 0.050 µg per mL of cadmium.

Procedure—Program the graphite furnace as follows: (1) dry at 120° using a 1-second ramp, a 55-second hold, and a 300 mL per minute argon flow; (2) char the sample at 850° using a 1-second ramp, a 30-second hold, and a 300 mL per minute air flow; (3) cool down, and purge the air from the furnace for 10 seconds using a 20° set temperature and a 300 mL per minute argon flow; (4) atomize at 2400° using a 0-second ramp and a 5-second hold with the argon flow stopped; and (5) clean out at 2600° with a 1-second ramp and a 5-second hold. Separately inject equal volumes (about 20 µL) of the *Test solutions* and the *Blank*, and 5 µL of the *Modifier working solution*, into the graphite tube of a suitable graphite furnace atomic absorption spectrophotometer equipped with a hollow cathode lamp for cadmium. Determine the peak area at the cadmium emission line at 228.8 nm, corrected for background absorption. Plot the corrected peak areas of the *Standard solutions* versus their contents of cadmium, in µg per mL, and calculate the regression line best fitting the points. Determine the concentration, *C*, in µg per mL, of cadmium in eachmL of the *Test solution* by interpolation from the regression line. Calculate the content of cadmium in the specimen taken by the formula:

$$25\ C/W,$$

in which *W* is the weight, in g, of Fish Oil taken to prepare the *Test solution:* not more than 0.1 µg per g is found.

Limit of mercury—Proceed as directed under *Method IIb* in the general chapter *Mercury* ⟨261⟩, except to use a *Standard Mercury Solution* having the equivalent of 0.025 µg per mL of mercury.

Test solution—Prepare as directed for the *Test solution* in the test for *Limit of arsenic*.

Limit of pesticides—Determine the content of polychlorinated dibenzo-*para*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), and total polychlorinated biphenyls (PCBs) using the Environmental Protection Agency's Method No. 1613, Revision B. The sum of polychlorinated dibenzo-*para*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) is not more than 2 pg of WHO toxic equivalent factors per g. The content of total polychlorinated biphenyls (PCBs) is not more than 0.09 µg per g.

Content of EPA and DHA—

Antioxidant solution—Dissolve an accurately weighed amount of butylated hydroxytoluene in hexanes to obtain a solution having a concentration of 0.05 mg per mL.

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Standard stock solution—Transfer 0.450 g of USP Cod Liver Oil RS accurately weighed, into a 10-mL volumetric flask, dissolve in *Antioxidant solution*, and dilute with the same solvent to volume.

Standard solution—Transfer 2.0 mL of the *Standard stock solution* into a quartz tube, and evaporate the solvent with a gentle stream of nitrogen. Add 1.5 mL of a 2% solution of sodium hydroxide in methanol, cap tightly with a polytetrafluoroethylene lined cap, mix, and heat in a water bath for 7 minutes. Cool, add 2 mL of boron trichloride-methanol solution, cover with nitrogen, cap tightly, mix, and heat in a water bath for 30 minutes. Cool to 40° to 50°, add 1 mL of isooctane, cap, and vortex or shake vigorously for at least 30 seconds. Immediately add 5 mL of saturated sodium chloride solution, cover with nitrogen, cap, and vortex or shake thoroughly for at least 15 seconds. Allow the upper layer to become clear, and transfer to a separate tube. Shake the methanol layer once more with 1 mL of isooctane, and combine the isooctane extracts. Wash the combined extracts with 2 quantities, each of 1 mL of water, and dry over anhydrous sodium sulfate.

System suitability mixture—Prepare a mixture having equal amounts, accurately weighed, of methyl palmitate, methyl stearate, methyl arachidate, and methyl behenate. [NOTE—A suitable mixture is available from Supelco, Bellefonte, Pa., as GLC-40, cat. number 1985-1AMP.]

Internal standard solution—Transfer an accurately weighed amount of USP Methyl Tricosanoate RS of about 70.0 mg to a 10-mL volumetric flask. Dissolve in isooctane, and dilute with the same solvent to volume.

Stock test solution—Transfer 0.300 g of Fish Oil Rich in Omega-3 Acids, accurately weighed, into a 10-mL volumetric flask, dissolve with *Antioxidant solution*, and dilute with the same solvent to volume.

Test solution 1—Proceed as directed for the *Standard solution*, using the *Stock test solution*.

Test solution 2— Transfer 1.0 mL of the *Internal standard solution* into a quartz tube. Then proceed as directed for *Test solution 1*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame ionization detector and a 0.25-mm × 30-m fused silica capillary column coated with a 0.25-µm film of G16. The temperature of the detector is maintained at 280° and that of the injection port at 250°. The column temperature is initially set at 170°, then increased at a rate of 1° per minute to 225°, and is maintained at 225° for 20 minutes. The carrier gas is helium with a split flow ratio of 1:200. Chromatograph the *Standard solution*, *System suitability mixture*, *Test solution 1*, and *Test solution 2*, and record the peak responses as directed for *Procedure:* the resolution between the peaks in the *Standard solution* due to methyl oleate and methyl *cis*-vaccinate is not less than 1.3, and between methyl gadoleate and methyl gondoate is sufficient for purposes of identification and area measurement. The theoretical area percentages for methyl palmitate, methyl stearate, methyl arachidate, and methyl behenate are 24.4, 24.8, 25.2, and 25.6, respectively. In a suitable instrument, the area percentages from the *System suitability mixture* are within 1% of the theoretical values. The number of fatty acid methyl ester peaks exceeding 0.05 percent of the total area in the chromatogram of the *Standard solution* is at least 24, and the 24 largest peaks of the methyl esters account for more than 90 percent of the total area. (These correspond to, in common elution order: 14:0, 15:0, 16:0, 16:1 n-7, 16:4 n-1, 18:0, 18:1 n-9, 18:1 n-7, 18:2 n-6, 18:3 n-3, 18:4 n-3, 20:1 n-11, 20:1 n-9, 20:1 n-7, 20:2 n-6, 20:4 n-6, 20:3 n-3, 20:4 n-3, 20:5 n-3, 22:1 n-11, 22:1 n-9, 21:5 n-3, 22:5 n-3, 22:6 n-3.)

Procedure—Separately inject duplicate equal volumes (about 1 µL) of the *Standard solution*, *Test solution 1*, and *Test solution 2* into the chromatograph, record the chromatograms, and measure the peak responses. Identify the retention times of the relevant fatty acids methyl esters by comparison of the chromatogram of the *Standard solution* with the reference chromatogram supplied with the USP Cod Liver Oil RS. Identify the retention time for the *Internal standard solution* by comparison of the chromatograms of *Test solution 1* and *Test solution 2*. Calculate the area percent for each fatty acid methyl ester taken by the formula:

$$100(r_A / r_B),$$

in which r_A is the average peak area of each individual fatty acid; and r_B is the total peak area from all peaks in the chromatogram, excepting the solvent front and butylated hydroxytoluene. Calculate the percentage of EPA or DHA in the Fish Oil Rich in Omega-3 Acids taken by the formula:

$$500FC(r_i / r_S)/1.04W,$$

in which 500 is the factor to express the content of DHA and EPA as free fatty acids in percentage, considering a 1 to 5 sample dilution; 1.04 is the factor to convert the methyl tricosanoate into tricosanoic acid; C is the concentration, in mg per mL, of the *Internal standard solution; W* is the weight, in mg, of the Fish Oil Rich in Omega-3 Acids taken to prepare the *Stock test solution; F* is the theoretical response factor of EPA or DHA, respectively, relative to the internal standard (0.99 for EPA and 0.97 for DHA); r_i is the peak response of either EPA or DHA in the chromatogram of *Test solution 2;* and r_S is the corrected peak response of the internal standard in *Test solution 2* calculated as follows:

$$[(r_{S2} / r_{EPA2}) - (r_{S1} / r_{EPA1})]\, r_{EPA2},$$

in which r_{S2} is the peak response of any peak at the locus of the internal standard in the chromatogram of *Test solution 2;* r_{S1} is the peak response of any peak at the locus of the internal standard in the chromatogram of *Test solution 1;* r_{EPA1} is the peak response of EPA in the chromatogram of *Test solution 1;* and r_{EPA2} is the peak response of EPA in the chromatogram of *Test solution 2*.■1S (*USP27*)

BRIEFING

Fish Oil Rich in Omega-3 Acids Capsules. Because there is no existing *USP* or *NF* monograph for this article, this new monograph is being proposed. See also the briefing under *Fish Oil Rich in Omega-3 Acids*.

(DSN: G. Giancaspro) RTS—39705-2

Add the following:

■Fish Oil Rich in Omega-3 Acids Capsules

» Fish Oil Rich in Omega-3 Acids Capsules contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of Fish Oil Rich in Omega-3 Acids. The oil contained in Fish Oil Rich in Omega-3 Acids Capsules conforms to the definition for *Fish Oil Rich in Omega-3 Acids*.

Packaging and storage—Preserve in tight containers at room temperature. Protect from light.

Labeling—The label states the amount of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in mg per Capsule.

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USP Reference standards ⟨11⟩—*USP Cod Liver Oil RS*. *USP Methyl Tricosanoate RS*.

Identification—Proceed as directed for *Identification* under *Fish Oil Rich in Omega-3 Acids*. The oil contained in the Capsules meets the requirements.

Weight variation ⟨2091⟩: meets the requirements.

Dissolution ⟨711 ⟩—

Medium: water; 500 mL.

Apparatus 2: 50 rpm.

Time: 15 minutes; 30 minutes.

Procedure—Place 1 Capsule in each vessel, and allow the Capsule to sink to the bottom of the vessel before starting rotation of the blade. Observe the Capsules, and record the time taken for each capsule shell to rupture.

Tolerances—The requirements are met if all of the Capsules tested rupture in not more than 15 minutes. If 1 or 2 of the Capsules rupture in more than 15 minutes but not more than 30 minutes, repeat the test on 12 additional Capsules. Not more than 2 of the total of 18 Capsules tested rupture in more than 15 minutes but not more than 30 minutes.

Other requirements—The contents of the Capsules meet the requirements of the tests for *Unsaponifiable matter*, *Acid value*, *Anisidine value*, *Total oxidation value*, *Heavy metals*, and *Pesticides* under *Fish Oil Rich in Omega-3 Acids*.

Content of fish oil—Accurately weigh not fewer than 10 Capsules in a tared weighing bottle. With a sharp blade, or by other appropriate means, carefully open the Capsules, without loss of shell material, and transfer the combined Capsule contents to a 100-mL beaker. Remove any adhering substance from the emptied Capsules by washing with several small portions of isooctane. Discard the washings, and allow the empty Capsules to dry in a current of dry air until the isooctane is completely evaporated. Weigh the empty Capsules in the original tared weighing bottle, and calculate the average net weight per capsule.

Content of DHA and EPA—Proceed as directed for *Content of DHA and EPA* under *Fish Oil Rich in Omega-3 Acids*.■1S (*USP27*)

BRIEFING

Maritime Pine, page 1903 of *PF* 28(6) [Nov.–Dec. 2002]; **Maritime Pine Extract,** page 1905 of *PF* 28(6) [Nov.–Dec. 2002]. It is proposed to revise the storage conditions in the *Packaging and storage* section.

(DSB: G. Giancaspro; PSD: C. Okeke) RTS—39821-1

Add the following:

■Maritime Pine

» Maritime Pine consists of the bark of stems of *Pinus pinaster* Aiton (*Pinus maritima* Poir.) Fam. Pinaceae. It contains not less than 8.0 percent and not more than 12.0 percent of procyanidins, calculated on the dried basis.

NOTE—This article is intended to be used in the preparation of extracts only and is not for direct human consumption.

Change to read:

Packaging and storage—Store at ~~room temperature.~~■25°, excursion permitted between 15° and 30°. Preserve in a well-closed container, and■1S (*USP27*) protect from moisture and excessive heat.

Labeling—The label states the Latin binomial and, following the official name, the part of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Maritime Pine Extract RS.*

Botanical characteristics—

Macroscopic—Bark pieces are typically 1 to 3 cm thick. The inner bark is plane to slightly concave, whitish to light brown, striped longitudinally; shiny and of slightly irregular surface, only a few millimeters thick. Abrupt change to a sequence of hard, convex, nearly parallel layers alternating with smooth, light brown layers. Up to 50 or more layers present, depending on the age of the bark. Outer surface of bark is dark reddish-brown composed of irregular scaly patches, with deep V-shaped fissures. Outer surface may also be gray, gray-green, or green-yellow due to presence of lichens.

Microscopic (*transverse section of bark*)—Light inner bark has irregular lateral stripes consisting of three to five cell layers of long, slender sieve cells with large pitted horizontal cell walls and large polygonal parenchyma cells containing single, irregular, rounded starch grain, 3 to 15 mm wide. Lateral stripes are separated from each other by ray parenchyma cells. Ray parenchyma cells are homogeneous in appearance, one to four cell layers thick and four and twenty cell layers high, each cell containing single, irregular, rounded starch grain, 3 to 15 mm wide. Cylindrical parenchyma cells with thin cell wall arranged in vertical rows with calcium oxalate prisms are also present. Outer part of the inner bark contains plate-shaped cells of undifferentiated periderm and older periderm with multiple layers of phellogen. The phellogen grows three to seven rows of phellum to the exterior and two to four rows of small cell phelloderm to the interior. The oldest and outermost part of the bark is composed of lignified sections of phelloderm and phellum cells, 15 to 35 mm thick, separated by collapsed phellogen. Phelloderm and phellum cells are up to 100 mm wide, square, rectangular, polygonal, or irregularly shaped. The cell walls are colorless. Phelloderm cells are moderately pitted with a reddish-brown content. Phellum cells have a thicker cell wall, strongly pitted, undulated contour, and a yellowish-brown to brownish-red content. Radially in between layers of phelloderm and phellum are layers of ray parenchyma cells, five to eight cells thick, rounded to radially stretched, thin walled, strongly pitted with collapsed cells and dead sieve cells.

Identification—

A: Pulverize 1 g of the dried Maritime Pine. Add 10 mg of the powdered material to 1 mL of methanol. Add 6 mL of a mixture of butanol and hydrochloric acid (95:5 v/v). Heat for 2 minutes in a water bath: the solution turns red.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Add 2 g of the powdered dried material to 20 mL of water. Place in a water bath for 20 minutes, and centrifuge. Extract the supernatant with 40 mL of ethyl acetate. Evaporate the ethyl acetate layer to dryness under a stream of nitrogen, with gentle heating. Dissolve the residue so obtained in 0.25 mL of alcohol.

Standard solution—Prepare a solution of USP Maritime Pine Extract RS in alcohol, having a concentration of about 25 mg per mL. [NOTE—Retain a portion of this solution for use in *Identification* test *C*.]

Application volume: 5 µL.

Developing solvent system: a mixture of ethyl acetate, methanol, and water (100:10:6).

Spray reagent: a mixture of alcohol and phosphoric acid (1:1), containing 1% of vanillin.

Procedure—Proceed as directed in the chapter, except to dry the plate with the aid of a current of air, spray with the *Spray reagent*, and dry at 110° for 10 minutes. A red band

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appears in the upper part of the chromatogram of the *Test solution*, at an R_F value of about 0.82, corresponding to a similar band in the chromatogram of the *Standard solution* (*presence of catechin*). The lower part of the chromatogram of the *Test solution* also shows red bands, at an R_F value of about 0.45 (*presence of oligomeric and polymeric procyanidins*). Two other red bands in the chromatogram of the *Test solution* correspond to those at similar R_F values in the chromatogram of the *Standard solution* (*presence of dimeric procyanidins*). A blue band appears in the chromatogram of the *Test solution* between the bands for catechin and the dimeric procyanidins, corresponding in color and R_F value to a similar band in the chromatogram of the *Standard solution*.

C: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Use the *Test solution* prepared as directed for *Identification* test *B*.

Standard solution 1—Use the *Standard solution* prepared as directed for *Identification* test *B*.

Standard solution 2—Prepare a solution of ferulic acid and protocatechuic acid containing 1 mg of each per mL.

Application volume: 10 µL.

Developing solvent system: a mixture of methylene chloride, methanol, and glacial acetic acid, and water (80:15:2:2).

Spray reagent—Prepare a 5% ferric chloride solution in methanol.

Procedure—Proceed as directed in the chapter, except to dry the plate at 110° and examine the plate under short-wavelength UV light. The upper third of the chromatogram of the *Test solution* exhibits three bands. The uppermost band is close to the solvent front. The middle third of the chromatogram of the *Test solution* exhibits a band corresponding in R_F value to the bands in the chromatograms of *Standard solution 1* and *Standard solution 2* (*presence of ferulic acid*). The lower third of the chromatogram of the *Test solution* exhibits a band corresponding to bands of similar R_F value in the chromatograms of *Standard solution 1* and *Standard solution 2* (*presence of protocatechuic acid*). A band near the origin is also visible in the chromatogram of the *Test solution*. Spray the plate with the *Spray reagent*, and dry at 110°. The bands due to ferulic acid and protocatechuic acid turn grayish-green and orange, respectively. A grayish-green band becomes visible in the chromatogram of the *Test solution* above the protocatechuic acid band (*presence of caffeic acid*). The band near the origin of the chromatogram of the *Test solution* turns orange.

Water content ⟨561⟩: not more than 35.0%.

Foreign organic matter ⟨561⟩: not more than 5%.

Total ash ⟨561⟩: not more than 1.5%.

Content of procyanidins—

Reagent solution A—Prepare a mixture of butanol and hydrochloric acid (95:5). [NOTE—Prepare this solution on the day of use.]

Reagent solution B—Dissolve 2 g of ferric ammonium sulfate in a mixture of 100 mL of water and 17.5 mL of hydrochloric acid. [NOTE—This solution can be used within 15 days of preparation.]

Test solution—Dry crushed Maritime Pine at 110° for 3 hours. Place about 1.9 g of the crushed material, accurately weighed, in a 20-mL vial, and add 10 mL of methanol. Crimp the vial and sonicate for 2 minutes. Heat in boiling water for 10 minutes. Cool to room temperature, allow the sediment to settle, and transfer the supernatant to a 100-mL volumetric flask, passing it through a filter having a 0.45-µm porosity. Wash the sediment two times with 10 mL of methanol, and transfer the solution into the same 100-mL

volumetric flask, again passing it through a filter having a 0.45-µm porosity. Dilute with methanol to volume, and mix. Transfer 1.0 mL of that solution into a 20-mL volumetric flask, dilute with methanol to volume, and mix.

Procedure—Transfer 1.0 mL of the *Test solution* and 1.0 mL of methanol to two separate 10-mL vials. To each flask add 6.0 mL of *Reagent solution A* and 0.25 mL of *Reagent solution B* to each flask. Seal the vials with crimp caps. Mix, and heat in a water bath for 40 minutes. Quickly cool to room temperature in an ice bath. Quantitatively transfer these solutions, with the aid of *Reagent solution A*, to two separate 10-mL volumetric flasks, dilute with *Reagent solution A* to volume, and mix. Determine the absorbance of the solution obtained from the *Test solution* at 546 nm, using the methanol-containing solution as the blank. Calculate the percentage of total procyanidins in the portion of Maritime Pine taken by the formula:

$$(2000A_U)/(36.7W),$$

in which A_U is the absorbance of the solution obtained from the *Test solution;* 36.7 is the absorptivity of the maritime pine procyanidins; and W is the weight, in g, of the Maritime Pine taken to prepare the *Test solution*.■2S (*USP27*)

BRIEFING

Maritime Pine Extract, page 1905 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Maritime Pine*.

(DSB: G. Giancaspro; PSD: C. Okeke) RTS—39821-2

Add the following:

■Maritime Pine Extract

» Maritime Pine Extract is prepared from the pulverized Maritime Pine using suitable solvents. It contains between 65 and 75 percent of procyanidins, calculated on the dried basis.

Change to read:

Packaging and storage— ~~Store in tight containers, protected from light.~~ ■Preserve in tight containers, and store at 25°, excursion permitted between 15° and 30°. Protect from light.■1S (*USP27*)

Labeling—The label states the official name of the article, the Latin binomial, and the part of the plant from which the article was prepared, in addition to the information required for *Labeling* under *Botanical extracts* ⟨565⟩.

USP Reference standards ⟨11⟩—*USP Maritime Pine Extract RS*.

Identification—

A: Dissolve 50 mg of Extract in 6 mL of a mixture of butanol and hydrochloric acid (95:5). Heat in a water bath for 2 minutes: the solution turns dark red.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Dissolve a quantity of Extract in methanol to obtain a solution having a concentration of about 25 mg per mL.

Standard solution 1—Prepare a solution of USP Maritime Pine Extract RS in methanol having a concentration of about 25 mg per mL.

Standard solution 2—Prepare a solution of ferulic acid in methanol having a concentration of about 1 mg per mL.

Application volume: 5 µL.

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Developing solvent system: a mixture of methylene chloride, methanol, glacial acetic acid, and water (80:15:2:2).

Spray reagent—Prepare a 5% ferric chloride solution in methanol.

Procedure—Proceed as directed in the chapter, except to dry the plate at 110° and to examine the plate under short-wavelength and long-wavelength UV light. The chromatogram of *Standard solution 1* exhibits bands in the middle third and upper third that correspond to protocatechuic acid and ferulic acid, respectively. Spray the plate with the *Spray reagent*, and dry at 110° for 10 minutes. The bands due to ferulic acid and protocatechuic acid turn grayish-green and orange, respectively. Grayish-green bands become visible in the chromatogram of *Standard solution 1* above and below protocatechuic acid indicating the presence of caffeic acid and catechin, respectively. The chromatogram of the *Test solution* exhibits bands due to caffeic acid, protocatechuic acid, and ferulic acid that correspond in color and R_F value to those in the chromatogram of *Standard solution 1*.

C: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Use the *Test solution* prepared as directed for *Identification* test *B*.

Standard solution—Use the *Standard solution 1* prepared as directed for *Identification* test *B*.

Application volume: 5 µL.

Developing solvent system: a mixture of ethyl acetate, formic acid, and water (100:10:6).

Spray reagent: a mixture of phosphoric acid and alcohol (1:1), containing 1% of vanillin.

Procedure—Proceed as directed in the chapter, except to spray the plate with the *Spray reagent*, and heat at 110° for 10 minutes. Three red bands appear in the middle third of the chromatogram of the *Standard solution* corresponding to two dimeric procyanidins and catechin. The chromatogram of the *Standard solution* also exhibits a blue band between the upper band due to upper dimeric procyanidins and the band due to catechin. The chromatogram of the *Test solution* contains bands that correspond to those found in the chromatogram of the *Standard solution*.

D: Proceed as directed in the following liquid-chromatographic procedure.

Solution A—Use filtered and degassed methanol.

Solution B—Carefully weigh 1 g of phosphoric acid, and dilute with water. Transfer to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Standard solution—Dissolve an accurately weighed quantity of USP Maritime Pine Extract RS in *Solution A* to obtain a solution having a known concentration of about 2 mg per mL. Pass through a membrane having a 0.45-µm or finer porosity.

Test solution—Weigh about 20 mg of Extract. Add 10 mL of *Solution A*, and sonicate for 10 minutes. Pass through a membrane having a 0.45-µm or finer porosity, discarding the first 4 mL of filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.6-mm × 15-cm column that contains base-deactivated packing L7 having less than 5-µm particle size. The column temperature is maintained at 40°. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	8	92	Equilibration
0–40	8→34	92→66	Linear gradient
40–45	34→2	66→98	Linear gradient
45–50	2	98	Isocratic
50–52	2→8	98→92	Linear gradient
52–57	8	92	Isocratic

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the chromatogram obtained is similar to the Reference Chromatogram provided with the USP Maritime Pine Extract RS; the resolution, *R*, between taxifolin and ferulic acid is not less than 3.0; and the tailing factor for taxifolin is not more than 2.0.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas for catechin, caffeic acid, taxifolin, and ferulic acid, identifying the peaks by comparison of the chromatogram of the *Standard solution* with the Reference Chromatogram: the chromatogram of the *Test solution* exhibits peaks for catechin, caffeic acid, taxifolin, and ferulic acid at the retention times corresponding to those in the chromatogram of the *Standard solution*.

Microbial limits ⟨2021⟩—The total aerobic microbial count does not exceed 10^4 per g, the total combined molds and yeasts count does not exceed 10^3 per g, and it meets the requirements of the tests for absence of *Salmonella* species, and *Escherichia coli*.

Loss on drying ⟨731⟩—Dry about 1.0 g of Extract, accurately weighed, for 3 hours at 110°: it loses not more than 8.0% of its weight.

Total ash ⟨561⟩: not more than 0.7%.

Pesticide residue ⟨561⟩: meets the requirement.

Limit of water-insoluble substances—Accurately weigh 0.50 g of Extract, and stir in 50 mL of water at 20° for 15 minutes. Pass through a fine sintered-glass filter, previously weighed. Dry the filter at 110° for 3 hours, cool to room temperature, and weigh the filter. Calculate the amount of water-insoluble material: not more than 10% of the amount of Extract taken.

Content of procyanidins—

Reagent solution A—Prepare a mixture of butanol and hydrochloric acid (95:5). [NOTE—Prepare this solution on the day of use.]

Reagent solution B—Dissolve 2 g of ferric ammonium sulfate in a mixture of 100 mL of water and 17.5 mL of hydrochloric acid. [NOTE—This solution can be used within 15 days of preparation.]

Test solution—Transfer about 0.125 g of Extract, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Transfer 1.0 mL of this solution to a 20-mL volumetric flask, dilute with methanol to volume, and mix.

Procedure—Transfer 1.0 mL of the *Test solution* and 1.0 mL of methanol to two separate 10-mL vials. To each flask add 6.0 mL of *Reagent solution A* and 0.25 mL of *Reagent solution B*. Seal the vials with crimp caps. Mix, and heat in a water bath for 40 minutes. Quickly cool to room temperature in an ice bath. Quantitatively transfer these solutions, with the aid of *Reagent solution A*, to two separate10-mL volumetric flasks, dilute with *Reagent solution A* to volume, and mix. Determine the absorbance of the solution obtained from the *Test solution* at 546 nm, using the methanol-containing solution as the blank. Calculate the percentage of total procyanidins in the portion of Extract taken by the formula:

$$(2000A_U)/(36.7W),$$

in which A_U is the absorbance of the solution obtained from the *Test solution;* 36.7 is the absorptivity of the maritime pine procyanidins; and W is the weight, in g, of the Extract taken to prepare the *Test solution*.

Other requirements—It meets the requirements for *Heavy metals* under *Botanical Extracts* ⟨565⟩. ■2S (*NF21*)

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BRIEFING

Nettle, page 105of *PF* 28(1) [Jan.–Feb. 2002]; **Powdered Nettle,** page 108 of *PF* 28(1) [Jan.–Feb. 2002]; **Powdered Nettle Extract,** page 109 of *PF* 28(1) [Jan.–Feb. 2002]. It is proposed to change the names of these monographs to Stinging Nettle, Powdered Stinging Nettle, and Powdered Stinging Nettle Extract, respectively. Although *Urica urens*, known in commerce as "dwarf nettle," may be present as a minor component of these articles, the predominant species is *Urtica dioica*. The proposed title change reflects the standard common name recognized in the American Herbal Products Association's *Herbs of Commerce* for the predominant species recognized in the monographs. Total amino acid is determined via a spectrophotometric procedure using glutamic and aspartic acids as reference standards. The gas chromatographic procedures used in the test for *Content of* β-*sitosterol* are based on analyses performed with the HP-1 brand of G2 column. Typical retention times for cholesterol and β-sitosterol are about 14 and 20 minutes, respectively. The gradient liquid chromatographic procedure used in the test for *Content of scopoletin* is based on analyses performed with the Kromasil C18 brand of L1 column. Typical retention times for scopoletin, cholesterol, and β-sitosterol are 12, 14, and 20 minutes, respectively.

(DSB: G. Giancaspro; NL: W. L. Paul) RTS—39963-1

Add the following:

■~~Nettle Nettles~~ Stinging Nettle

» ~~Nettle Nettles~~ Stinging Nettle consists of dried roots and rhizomes of *Urtica dioica* ~~(Linné)~~ L. ssp dioica. (Fam. Urticaceae), ~~known in commerce as stinging nettle,~~ and may contain *Urtica urens* ~~(Linné),~~ L., known in commerce as dwarf nettle, ~~their hybrids, or mixtures of them~~ as a minor component. It contains not less than 0.8 percent of total amino acids, not less than 0.05 percent of β-sitosterol ($C_{29}H_{50}O$), and not less than 3 µg per g of scopoletin ($C_{10}H_8O_4$), calculated on the dried basis.

Packaging and storage—~~Store~~ Preserve in tight containers, protected from light. ~~moisture, and excessive heat.~~ Store at controlled room temperature.

Labeling—The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Aspartic Acid RS. USP Glutamic Acid RS. USP Scopoletin RS. USP* β-*Sitosterol RS.*

Botanic characteristics—

Macroscopic—The rhizome is irregularly bent, about 3 to 10 mm thick, and light gray-brown on the outside; thin roots spring from the knotty bulges of a lengthwise furrow. A transverse cut of the rhizome shows it is fibrous, light yellowish white, and usually has a small medulla cave. The roots are often very long, usually 0.5 to 2 mm thick, light yellow-brown on the outside, and contain some deep longitudinal furrows; a transverse cut shows a pale and almost pure-white color.

Histology—The transverse section of the rhizome and root shows the following characteristics. The rhizome has a narrow cork composed of brown, thin-walled cells, a few rows of tangentially elongated cortical parenchyma, and a pericyclic region with numerous fibers occurring singly or, more frequently, in small groups. Fibers are much elongated with very thick and lignified walls. Some cells of the pericycle and outer part of secondary phloem contain large globular compound crystals of calcium oxalate. The vascular cambial region is distinct and continuous with narrow radial groups of vascular tissue separated by wide medullary rays. The secondary phloem is mainly parenchymatous with groups of thin-walled sieve tissue. The xylem is dense and completely lignified, containing scattered vessels, isolated or in small groups, associated with moderately thickened xylem parenchyma cells and numerous thicker-walled xylem fibers with slit-shaped pits. Individual vessels have fairly large, closely arranged, bordered pits, while the adjacent parenchyma has simple

or bordered pits. Medullary rays indicate alternating areas of lignified and unlignified cells, appearing as tangential bands between the vascular bundles, each composed of five or six layers of cells; the lignified cells have moderately thickened walls with simple pits. The pith is composed of rounded, unlignified parenchyma, collapsed in the central part to form a cavity. Mature roots show a thin cork, narrow phelloderm, and secondary phloem and xylem with alternating areas of lignified and unlignified parenchyma in the wide medullary rays, similar to that found in the rhizome.

Identification, *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent: 0.50-mm layer of chromatographic silica gel mixture.

Test solution—Extract 1 g of powder by refluxing with 10 mL of a solution containing toluene, ethyl acetate, and methanol (7:2:1) for 15 minutes, cool, and filter. Evaporate the filtrate to dryness under reduced pressure at less than 40°, and dissolve the residue in 2 mL of the toluene, ethyl acetate, methanol solution.

Standard solution—Dissolve an accurately weighed quantity of USP Scopoletin RS and USP β-Sitosterol RS in methanol to obtain a solution having a known concentration of 0.05 and 0.5 mg per mL, respectively.

Application volume: 20 µL for the *Test solution;* 10 µL for the *Standard solution*.

Developing solvent system: diethyl ether and methanol (9:1).

Procedure—Proceed as directed in the chapter. Examine the plates under UV light at 365 nm. Spray the plate with about 10 mL of a mixture of water, 85% phosphoric acid, and 10% vanillin in 96% ethanol (4.5:4.5:1); heat between 100° and 105° for 10 minutes; and examine under daylight. The chromatogram of the *Test solution* exhibits a violet-red zone corresponding to the β-sitosterol peak at the same R_F value as the β-sitosterol peak in the chromatogram of the *Standard solution*. Weakly violet-red zones above and below β-sitosterol, corresponding to β-sitosterol-glucoside, are visible.

Microbial limits ⟨2021⟩—The total aerobic microbial count does not exceed ~~10^7~~ 10^6 cfu per g, the total combined molds and yeasts count does not exceed ~~10^5~~ 10^4 cfu per g, ~~the coliform count does not exceed 10^4 cfu per g,~~ and the ~~enterobacterial~~ bile-tolerant Gram-negative bacteria count does not exceed ~~10^4~~ 10^3 cfu per g. It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.*~~and *Staphylococcus aureus.*~~

Loss on drying ⟨731⟩—Dry 1.0 g of ~~Nettle Nettles~~ Stinging Nettle, finely powdered, at 105° for 2 hours: it loses not more than 12.0% of its weight.

Foreign organic matter ⟨561⟩: not more than 2.0%.

Total ash ⟨561⟩: not more than 10%.

Pesticide residues ⟨561⟩: meets the requirements.

Content of total amino acids—

pH 5.5 Acetate buffer—Mix 5.40 g of anhydrous sodium acetate, 0.3 mL of glacial acetic acid, and water to a final volume of 100 mL.

Reagent solution—Prepare a solution containing about 1.00 g of ninhydrin, 1.50 g of hydrindantin, and 37.5 mL of propylene glycol, and adjust with *pH 5.5 Acetate buffer* to 50.0 mL. [NOTE—Prepare the *Reagent solution* daily.]

Standard solution—Dissolve accurately weighed quantities of USP Glutamic Acid RS and USP Aspartic Acid RS in water to obtain a solution having a known concentration of about 0.1 mg of each per mL.

Test solution—Finely powder an amount of ~~Nettle Nettles~~ Stinging Nettle, and transfer about 1.0 g, accurately weighed, to 80 mL of water. Place in an ultrasonic bath

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for 25 minutes, and centrifuge. Transfer the supernatant to a 100-mL volumetric flask, dilute with water to volume, and filter.

Procedure—Transfer 5.0 mL of the *Test solution* and 1.0 mL of the *Standard solution* to two separate, appropriately labeled, 50-mL volumetric flasks. Add 4.0 mL of water to the *Standard solution* and 5.0 mL of *Reagent solution* to both the *Test solution* and the *Standard solution*. Heat in a boiling water bath for 30 minutes, cool, and adjust with a mixture of ethanol and water (1:1) to volume. Concomitantly determine the absorbances of the *Standard solution* and the *Test solution* in 1-cm cells at the wavelength of maximum absorbance at about 570 nm with a suitable spectrophotometer. Prepare a blank using 5.0 mL of water, and treat similarly to the *Test solution*. Calculate the percentageof total amino acids in the portion of ~~Nettle Nettles~~ Stinging Nettle taken by the formula:

$$2000(A_U / A_S)(W_S / W_U),$$

in which A_U and A_S are the absorbances of the *Test solution* and the *Standard solution*, respectively; W_S is the sum of the weights, in mg, of USP Glutamic Acid RS and USP Aspartic Acid RS, calculated on the dried basis, in the *Standard solution;* and W_U is the weight, in mg, of dried ~~Nettle Nettles~~ Stinging Nettle in the *Test solution:* not less than 0.8% of total amino acids is found.

Content of β-sitosterol—

Derivatizing reagent—Prepare a solution containing equal volumes (1:1:1) of BSTFA [*N*,*O*-bis(trimethylsilyl)trifluoroacetamide], anhydrous pyridine, and a mixture of BSA [*N*,*O*-(trimethylsilyl)acetamide], TMSI (*N*-trimethylsilyimidazole), and TMCS (trimethylchlorosilane) (3:3:2).

Internal standard solution—Dissolve an accurately weighed quantity of cholesterol in chloroform to obtain a solution having a known concentration of about 10 mg per mL.

Standard solution—Dissolve 50 mg of USP β-Sitosterol RS, accurately weighed, in 2.0 mL of chloroform, add 1 mL of *Internal standard solution*, and dilute with chloroform to 5 mL. Transfer 0.5 mL of this solution to a 10-mL round-bottomed flask, dry the solvent under reduced pressure, add 1 mL of *Derivatizing reagent*, and mix.

Test solution—Finely powder an amount of ~~Nettle Nettles~~ Stinging Nettle, transfer 50.0 g to a Soxhlet apparatus, treat with chloroform, and extract for 6 hours. The volume of chloroform used is at least twice the volume of the thimble with an appropriate-size flask. Dry the solvent under reduced pressure, add 1.0 mL of *Internal standard solution*, and dilute with chloroform to 10 mL. Transfer 0.5 mL of this solution to a 10-mL round-bottomed flask, dry the solvent under reduced pressure, and add 0.5 mL of *Derivatizing reagent*.

Chromatographic system (see *Chromatography*⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.20-mm × 25-m fused-silica capillary column coated with a 0.35-µm film of phase G2. The carrier gas is helium, flowing at a rate of about 0.5 mL per minute. The injection port and detector temperatures are maintained at 325°. The column temperature is initially held at 300°, and maintained at this temperature for 60 minutes. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the tailing factor for each sterol peak is not more than 2.0; and the relative standard deviation for replicate injections determined from each sterol peak is not more than 5.0%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses of the sterols. Calculate the percentage of β-sitosterol in the portion of ~~Nettle Nettles~~ Stinging Nettle taken by the formula:

$$100(R_U/R_S)(C_S/C_U),$$

in which R_U and R_S are the peak response ratios of β-sitosterol to the internal standard obtained from the *Standard solution* and the *Test solution*, respectively; C_S is the concentration, in mg per mL, of USP β-Sitosterol RS in the *Standard solution;* and C_U is the concentration, in mg per mL, of ~~Nettle Nettles~~ Stinging Nettle in the *Test solution:* not less than 0.05% of β-sitosterol is found.

Content of scopoletin—

Solution A—Use water.

Solution B—Use methanol.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Scopoletin RS in methanol to obtain a solution having a known concentration of about 0.02 µg per mL.

Test solution—Finely powder an amount of ~~Nettle Nettles~~ Stinging Nettle, and mix 4.000 g, accurately weighed, with 25 mL of methanol. Place in an ultrasonic bath for 25 minutes, and centrifuge. Transfer 0.5 mL of the solution to a 10-mL volumetric flask, and dilute with methanol to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a fluorescence detector set at an excitation wavelength of 366 nm and an emission wavelength of 420 nm and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	75	25	equilibration
0–2	75→60	25→40	linear gradient
2–8	60	40	isocratic
8–10	60→0	40→100	linear gradient
10–15	0	100	isocratic
15–20	0→75	100→25	linear gradient
20–30	75	25	isocratic

Chromatograph about 10 µL of the *Standard solution*, and record the peak responses as directed for *Procedure:* the capacity factor (k') determined from the scopoletin peak is not less than 5; the tailing factor for the scopoletin peak is not more than 2.0; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for scopoletin. Calculate the content of scopoletin ($C_{10}H_8O_4$), in µg per g, in the portion of ~~Nettle Nettles~~ Stinging Nettle taken by the formula:

$$10{,}000(r_U/r_S)(C_S/C_U),$$

in which r_U and r_S are the peak responses of scopoletin in the *Test solution* and the *Standard solution*, respectively; C_S is the concentration, in mg per mL, of USP Scopoletin RS in the *Standard solution;* and C_U is the concentration, in mg per mL, of ~~Nettle Nettles~~ Stinging Nettle in the *Test solution:* not less than 3 µg per g of scopoletin is found. ■1S (*USP27*)

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BRIEFING

Powdered Nettle, page 108 of *PF* 28(1) [Jan.–Feb. 2002]—See briefing under *Nettle.*

(DSB: G. Giancaspro) RTS—39963-2

Add the following:

■Powdered ~~Nettle Nettles~~ Stinging Nettle

» Powdered ~~Nettle Nettles~~ Stinging Nettle is ~~Nettle Nettles~~ Stinging Nettle reduced to a fine or very fine powder.

Packaging and storage—Store in tight containers, protected from light and ~~moisture~~ excessive heat.

Labeling—The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Aspartic Acid RS*. *USP Glutamic Acid RS*. *USP Scopoletin RS*. *USP* β-*Sitosterol RS*.

Botanic characteristics—[NOTE—The test is carried out under a microscope using chloral hydrate solution.] The powder is yellowish to brownish gray, and shows several fragments of net and dot vessels with a strongly varying diameter, usually between 50 and 150 µm. Few, if any, dotted bast fibers are present. Clearly dotted wood fibers, about 200 to 800 µm in length, thin-walled parenchyma cells, sometimes with calcium oxalate glands and occasionally with single crystals and fragments of cork consisting of flat-shaped, thin-walled cells are also present.

Other requirements—It meets the requirements of the tests for *Identification*, *Microbial limits*, *Foreign organic matter*, *Total ash*, *Pesticide residues*, *Content of total amino acids, Content of* β-*sitosterol*, and *Content of scopoletin* under ~~*Nettle Nettles*~~ *Stinging Nettle.* ■1S (*USP27*)

BRIEFING

Powdered Nettle Extract, page 109 of *PF* 28(1) [Jan.–Feb. 2002]—See briefing under *Nettle*.

(DSB: G. Giancaspro) RTS—39963-3

Add the following:

■Powdered ~~Nettle Nettles~~ Stinging Nettle Extract

» Powdered ~~Nettle Nettles~~ Stinging Nettle Extract is prepared from comminuted Stinging Nettle with 60 percent alcohol or other suitable solvents. It contains not less than 5.0 percent of total amino acids, not less than 0.1 percent of β-sitosterol ($C_{29}H_{50}O$) and not less than 30 µg per g of scopoletin ($C_{10}H_8O_4$). The ratio of the starting crude plant material to Powdered Extract is 10:1.

Packaging and storage—Store in tight containers, protected from light ~~and moisture~~ at controlled room temperature.

Labeling—The label states the official name of the article, the Latin binomial, and, following the official name, the part of the plant from which the article was prepared. Label it to

indicate the content of total amino acids, β-sitosterol, scopoletin, the extracting solvent used for preparation, and the ratio of the starting crude plant material to Powdered Extract.

USP Reference standards ⟨11⟩—*USP Aspartic Acid RS*. *USP Glutamic Acid RS*. *USP Scopoletin RS*. *USP* β-*Sitosterol RS*.

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent, *Standard solution*, *Application volume*, *Developing solvent system*, and *Procedure*—Proceed as directed for the test for *Identification* under ~~*Nettle Nettles.*~~ *Stinging Nettle.*

Test solution—Dissolve 0.6 g of Powdered Extract, accurately weighed, in a mixture of toluene, ethyl acetate, and methanol (7:2:1), filter, and dry under reduced pressure at a temperature below 40°. Dissolve the residue in 2.0 mL of the toluene, ethyl acetate, and methanol mixture.

B: The retention time of β-sitosterol in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *Standard solution*, as obtained in the test for *Content of* β-*sitosterol*.

C: The retention time of scopoletin in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *Standard solution*, as obtained in the test for *Content of scopoletin.*

Microbial limits ⟨2021⟩—The total aerobic microbial count does not exceed ~~10^4~~ 10^3 cfu per g, the total combined molds and yeasts count does not exceed ~~10^2~~ 10^2 cfu per g. ~~the coliform count does not exceed 10^2 cfu,~~ It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*. ~~*Staphylococcus aureus.*~~

Loss on drying ⟨731⟩—Dry about 1.0 g of Powdered Extract, accurately weighed, at 105° for 2 hours: it loses not more than 8.0% of its weight.

Total ash ⟨561⟩: not more than 20.0%.

Pesticide residues ⟨561⟩: meets the requirements.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Alcohol content, *Method II* ⟨611⟩ (*if present*): not more than 1.0%.

Content of total amino acids—

pH 5.5 Acetate buffer, *Reagent solution*, and *Standard solution*—Proceed as directed for *Content of total amino acids* under ~~*Nettle Nettles*~~ *Stinging Nettle.*

Test solution—Dissolve 50 mg of Powdered Extract, accurately weighed, in 80 mL of water, shake for 10 minutes, dilute with water to 100 mL, and filter.

Procedure—Proceed as directed for *Content of total amino acids* under ~~*Nettle Nettles*~~ *Stinging Nettle,* except to calculate the percentage of total amino acids taken by the formula:

$$2000(A_U/A_S)(W_S/W_U),$$

in which W_U is the weight, in mg, of the Powdered Extract in the *Test solution;* and the other terms are as defined therein: not less than 5.0% of total amino acids is found.

Content of β-sitosterol—

Derivatizing reagent, *Internal standard solution*, *Standard solution*, and *Chromatographic system*—Proceed as directed for *Content of* β-*sitosterol* under ~~Nettle Nettles~~ *Stinging Nettle.*

Test solution—Transfer 20.0 g of Powdered Extract, accurately weighed, to a Soxhlet apparatus, treat with chloroform, and extract for 6 hours. The volume of chloroform used is at least twice the volume of the thimble with an appropriate-size flask. Dry the solvent under reduced pressure, add 1.0 mL of *Internal standard solution*, and dilute with

In-Process Revision

chloroform to 10 mL. Transfer 0.5 mL of this solution to a 10-mL round-bottomed flask, dry the solvent under reduced pressure, and add 0.5 mL of *Derivatizing reagent*.

Procedure—Proceed as directed for *Content of* β*-sitosterol* under ~~Nettle Nettles~~ *Stinging Nettle*, except to calculate the percentage of β-sitosterol in the portion of Powdered Extract taken by the formula:

$$100(R_U / R_S)(C_S / C_U),$$

in which C_U is the concentration, in mg per mL, of Powdered Extract in the *Test solution;* and the other terms are as defined therein: not less than 0.1% of β-sitosterol is found.

Content of scopoletin—

Solution A, *Solution B*, *Mobile phase*, *Standard solution*, and *Chromatographic system*—Proceed as directed for *Content of scopoletin* under ~~Nettle Nettles~~ *Stinging Nettle.*

Test solution—Dissolve 200 mg of Powdered Extract, accurately weighed, in 25 mL of methanol, place in an ultrasonic bath for 25 minutes, and centrifuge. Transfer 0.5 mL of this solution to a 10-mL volumetric flask, and dilute with methanol to volume.

Procedure—Proceed as directed for *Content of scopoletin* under ~~Nettle Nettles~~ *Stinging Nettle,* except to calculate the content of scopoletin ($C_{10}H_8O_4$) in the portion of Powdered Extract taken by the formula:

$$10{,}000(r_U / r_S)(C_S / C_U),$$

in which C_U is the concentration, in mg per mL of Powdered Extract in the *Test solution;* and the other terms are as defined therein: not less than 30 µg per g of scopoletin is found.■1S (*USP27*)

BRIEFING

Saw Palmetto Capsules, page 3025 of the *First Supplement.* It is proposed to revise the Definition to reflect the same ratio of lauric acid to caprylic acid presented in the monograph for *Saw Palmetto Extract*.

(DSB: G. Giancaspro) RTS—39827-1

Change to read:

» Saw Palmetto Capsules contain Saw Palmetto Extract. Capsules contain not less than 22.0 percent of lauric acid and not more than 34.0 percent of the labeled amount of Saw Palmetto Extract. The ratio of the concentrations of lauric acid to caprylic acid is not less than ~~10~~

■8.5■1S (*USP27*)

and not more than 17.5. The ratio of the concentrations of lauric acid to myristic acid is not less than 2.2 and not more than 2.8.

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"—See PF Vol. 28 No. 6, page 1757.
Preservation, Packaging, Storage, and Labeling—See PF Vol. 28 No. 4, page 1061.
Significant Figures and Tolerances—See PF Vol. 28 No. 5, page 1379.
Tests and Assays—See PF Vol. 28 No. 5, page 1380.

USP MONOGRAPHS

Acebutolol Hydrochloride—See PF Vol. 27 No. 3, page 2493.
Acebutolol Hydrochloride Capsules—See PF Vol. 27 No. 1, page 1743.
Acepromazine Maleate—See PF Vol. 27 No. 3, page 2493.
Acepromazine Maleate Injection—See PF Vol. 27 No. 3, page 2494.
Acepromazine Maleate Tablets—See PF Vol. 27 No. 3, page 2494.
Acetaminophen—See PF Vol. 27 No. 3, page 2494.
Acetaminophen Capsules—See PF Vol. 27 No. 3, page 2494.
Acetaminophen for Effervescent Oral Solution—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Oral Solution—See PF Vol. 27 No. 3, page 2494.
Acetaminophen Oral Suspension—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Suppositories—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Tablets—See PF Vol. 27 No. 3, page 2495.
Acetaminophen and Aspirin Tablets—See PF Vol. 27 No. 3, page 2495.
Acetaminophen, Aspirin, and Caffeine Tablets—See PF Vol. 27 No. 3, page 2495.
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 3, page 2496.
Oral Powder Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 3, page 2496.
Oral Solution Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 6, page 3241.
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 3, page 2496.
Acetaminophen and Codeine Phosphate Capsules—See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Oral Solution—See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Oral Suspension—See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Tablets—See PF Vol. 29 No. 3, page 602.
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution—See PF Vol. 27 No. 3, page 2499.
Acetaminophen and Diphenhydramine Citrate Tablets—See PF Vol. 27 No. 3, page 2499.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 27 No. 3, page 2499.
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 27 No. 3, page 2500.
Acetazolamide—See PF Vol. 27 No. 3, page 2500.
Acetazolamide for Injection—See PF Vol. 27 No. 3, page 2500.
Acetazolamide Tablets—See PF Vol. 27 No. 3, page 2501.
Glacial Acetic Acid—See PF Vol. 27 No. 3, page 2501.
Acetic Acid Irrigation—See PF Vol. 27 No. 3, page 2501.
Acetic Acid Otic Solution—See PF Vol. 27 No. 3, page 2501.
Acetohexamide—See PF Vol. 27 No. 3, page 2501.
Acetohexamide Tablets—See PF Vol. 27 No. 3, page 2501.
Acetohydroxamic Acid Tablets—See PF Vol. 27 No. 3, page 2503.
Acetylcholine Chloride—See PF Vol. 27 No. 3, page 2502.
Acetylcholine Chloride for Ophthalmic Solution—See PF Vol. 27 No. 3, page 2502.
Acetylcysteine—See PF Vol. 27 No. 3, page 2503.
Acetylcysteine Solution—See PF Vol. 27 No. 3, page 2503.
Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution—See PF Vol. 27 No. 3, page 2503.
Acyclovir—See PF Vol. 29 No. 3, page 602.
Acyclovir Capsules—See PF Vol. 29 No. 3, page 602.
Acyclovir for Injection—See PF Vol. 29 No. 3, page 602.
Acyclovir Ointment—See PF Vol. 29 No. 3, page 604.
Acyclovir Oral Suspension—See PF Vol. 29 No. 3, page 604.
Acyclovir Tablets—See PF Vol. 29 No. 3, page 604.
Adenine—See PF Vol. 27 No. 3, page 2504.
Albendazole—See PF Vol. 27 No. 3, page 2505.
Albendazole Oral Suspension—See PF Vol. 27 No. 3, page 2505.
Albendazole Tablets—See PF Vol. 27 No. 3, page 2505.
Albumin Human—See PF Vol. 29 No. 1, page 43.
Albuterol—See PF Vol. 27 No. 3, page 2505.
Albuterol Sulfate—See PF Vol. 27 No. 3, page 2506.
Albuterol Tablets—See PF Vol. 27 No. 3, page 2506.
Alclometasone Dipropionate—See PF Vol. 27 No. 3, page 2506.
Alclometasone Dipropionate Cream—See PF Vol. 27 No. 3, page 2507.
Alclometasone Dipropionate Ointment—See PF Vol. 27 No. 3, page 2507.
Alcohol—See PF Vol. 27 No. 3, page 2507.
Dehydrated Alcohol—See PF Vol. 27 No. 3, page 2507.
Dehydrated Alcohol Injection—See PF Vol. 27 No. 3, page 2507.
Rubbing Alcohol—See PF Vol. 27 No. 3, page 2507.
Alcohol in Dextrose Injection—See PF Vol. 27 No. 3, page 2508.
Alendronate Sodium—See PF Vol. 28 No. 3, page 737.
Alendronate Sodium Tablets—See PF Vol. 28 No. 3, page 740.
Allopurinol—See PF Vol. 28 No. 5, page 1387.
Allopurinol Tablets—See PF Vol. 29 No. 3, page 604.
Allyl Isothiocyanate—See PF Vol. 27 No. 3, page 2509.
Alprazolam—See PF Vol. 27 No. 3, page 2509.
Alprazolam Tablets—See PF Vol. 27 No. 3, page 2509.
Alprostadil—See PF Vol. 29 No. 2, page 392.
Alprostadil Injection—See PF Vol. 28 No. 5, page 1389.
Altretamine—See PF Vol. 27 No. 3, page 2514.
Altretamine Capsules—See PF Vol. 27 No. 3, page 2514.
Potassium Alum—See PF Vol. 27 No. 3, page 2515.
Alumina and Magnesia Oral Suspension—See PF Vol. 27 No. 3, page 2515.
Alumina and Magnesia Tablets—See PF Vol. 27 No. 3, page 2515.
Alumina, Magnesia, and Calcium Carbonate Oral Suspension—See PF Vol. 27 No. 6, page 3241.
Alumina, Magnesia, and Calcium Carbonate Tablets—See PF Vol. 27 No. 3, page 2515.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—See PF Vol. 27 No. 6, page 3241.
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—See PF Vol. 29 No. 3, page 605.
Amoxicillin Tablets—See PF Vol. 29 No. 1, page 48.
Amoxicillin and Clavulanate Potassium for Oral Suspension—See PF Vol. 29 No. 3, page 605.
Amoxicillin and Clavulanate Potassium Tablets—See PF Vol. 29 No. 3, page 605.
Amphetamine Sulfate—See PF Vol. 28 No. 3, page 744.
Ampicillin—See PF Vol. 28 No. 6, page 1766.
Ampicillin Capsules—See PF Vol. 28 No. 6, page 1766.

Ampicillin for Injectable Suspension—See PF Vol. 28 No. 6, page 1766.
Ampicillin Tablets—See PF Vol. 28 No. 6, page 1767.
Amprolium Oral Solution—See PF Vol. 29 No. 3, page 606.
L-Asparagine—See PF Vol. 29 No. 3, page 687.
Aspartic Acid—See PF Vol. 28 No. 5, page 1391.
Aspirin and Codeine Phosphate Tablets—See PF Vol. 29 No. 3, page 606.
Astemizole Tablets—See PF Vol. 28 No. 3, page 745.
Atenolol Tablets—See PF Vol. 29 No. 1, page 49.
Atenolol and Chlorthalidone Tablets—See PF Vol. 29 No. 3, page 606.
Atovaquone Oral Suspension—See PF Vol. 29 No. 1, page 49.
Azithromycin—See PF Vol. 29 No. 1, page 50.
Azithromycin Capsules—See PF Vol. 27 No. 6, page 3394.
Barium Sulfate Paste—See PF Vol. 25 No. 4, page 8479.
Benazepril Hydrochloride—See PF Vol. 28 No. 6, page 1768.
Benazepril Hydrochloride Tablets—See PF Vol. 29 No. 3, page 606.
Benzethonium Chloride Concentrate—See PF Vol. 29 No. 3, page 608.
Benztropine Mesylate Tablets—See PF Vol. 28 No. 5, page 1392.
Betahistine Hydrochloride—See PF Vol. 26 No. 5, page 1401.
Betamethasone—See PF Vol. 28 No. 6, page 1772.
Betamethasone Cream—See PF Vol. 28 No. 6, page 1773.
Betamethasone Acetate—See PF Vol. 28 No. 6, page 1773.
Bethanechol Chloride—See PF Vol. 29 No. 1, page 52.
Bethanechol Chloride Tablets—See PF Vol. 29 No. 1, page 54.
Bismuth Subsalicylate Oral Suspension—See PF Vol. 28 No. 2, page 627.
Bismuth Subsalicylate Tablets—See PF Vol. 28 No. 5, page 1603.
Bisoprolol Fumarate—See PF Vol. 29 No. 3, page 609.
Bisoprolol Fumarate Tablets—See PF Vol. 29 No. 3, page 610.
Bisoprolol Fumarate and Hydrochlorothiazide Tablets—See PF Vol. 29 No. 3, page 612.
Brinzolamide Ophthalmic Suspension—See PF Vol. 28 No. 6, page 1774.
Bromodiphenhydramine Hydrochloride and Codeine Phosphate Syrup—See PF Vol. 27 No. 5, page 2980.
Bromodiphenhydramine Hydrochloride Elixir—See PF Vol. 28 No. 6, page 1776.
Bromodiphenhydramine Hydrochloride Oral Solution—See PF Vol. 28 No. 6, page 1777.
Butalbital, Acetaminophen, and Caffeine Tablets—See PF Vol. 29 No. 3, page 615.
Calcium Carbonate Lozenges—See PF Vol. 28 No. 6, page 1778.
Calcium Carbonate Tablets—See PF Vol. 28 No. 5, page 1392.
Dibasic Calcium Phosphate—See PF Vol. 22 No. 6, page 3029.
Anhydrous Dibasic Calcium Phosphate—See PF Vol. 22 No. 6, page 2011.
Carbidopa and Levodopa Tablets—See PF Vol. 29 No. 3, page 615.
Cefaclor Capsules—See PF Vol. 29 No. 1, page 56.
Cefazolin Ophthalmic Solution—See PF Vol. 28 No. 2, page 261.
Cefipime for Injection—See PF Vol. 28 No. 6, page 1778.
Cefixime—See PF Vol. 29 No. 3, page 616.
Ceftazidime for Injection—See PF Vol. 29 No. 3, page 617.
Cefuroxime Axetil for Oral Suspension—See PF Vol. 28 No. 6, page 1780.
Cephalexin Tablets for Oral Suspension—See PF Vol. 28 No. 6, page 1782.
Ciclopirox—See PF Vol. 29 No. 2, page 393.
Ciclopirox Olamine—See PF Vol. 29 No. 2, page 395.
Cimetidine Tablets—See PF Vol. 28 No. 1, page 52.
Clavulanate Potassium—See PF Vol. 29 No. 3, page 617.
Clindamycin Phosphate—See PF Vol. 29 No. 1, page 57.
Clindamycin Phosphate Topical Solution—See PF Vol. 28 No. 5, page 1393.
Clindamycin Phosphate Vaginal Inserts—See PF Vol. 29 No. 3, page 620.
Clonazepam Tablets—See PF Vol. 29 No. 3, page 621.
Clonidine—See PF Vol. 29 No. 1, page 58.
Clonidine Hydrochloride Injection—See PF Vol. 26 No. 2, page 351.
Clonidine Transdermal System—See PF Vol. 28 No. 2, page 265.
Clotrimazole Vaginal Inserts—See PF Vol. 29 No. 3, page 622.
Clotrimazole Vaginal Tablets—See PF Vol. 29 No. 3, page 623.
Clotrimazole and Betamethasone Dipropionate Cream—See PF Vol. 29 No. 3, page 623.
Clozapine—See PF Vol. 29 No. 3, page 623.
Cod Liver Oil Capsules—See PF Vol. 29 No. 3, page 623.
Corticotropin Injection—See PF Vol. 28 No. 6, page 1783.
Corticotropin for Injection—See PF Vol. 28 No. 6, page 1784.
Cyanocobalamin Co 57 Capsules—See PF Vol. 29 No. 2, page 397.
Cyanocobalamin Co 57 Oral Solution—See PF Vol. 29 No. 2, page 398.
Cyclandelate—See PF Vol. 26 No. 2, page 353.
Cyclosporine Capsules—See PF Vol. 27 No. 4, page 2721.
Demeclocycline Hydrochloride Capsules—See PF Vol. 29 No. 3, page 625.
Demeclocycline Hydrochloride Tablets—See PF Vol. 29 No. 3, page 625.
Desmopressin Acetate—See PF Vol. 24 No. 2, page 5773.
Desmopressin Injection—See PF Vol. 24 No. 2, page 5778.
Desmopressin Nasal Spray Solution—See PF Vol. 24 No. 2, page 5779.
Desogestrel—See PF Vol. 28 No. 6, page 1785.
Desogestrel and Ethinyl Estradiol Tablets—See PF Vol. 28 No. 5, page 1394.
Dexamethasone Injection—See PF Vol. 28 No. 5, page 1402.
Dextran 1—See PF Vol. 28 No. 6, page 1787.
Dextran 40—See PF Vol. 29 No. 2, page 399.
Dextran 70—See PF Vol. 29 No. 2, page 401.
Dextroamphetamine Sulfate—See PF Vol. 28 No. 3, page 751.
Diethylstilbestrol Diphosphate Tablets—See PF Vol. 23 No. 1, page 3385.
Digoxin Tablets—See PF Vol. 28 No. 1, page 55.
Dihydroergotamine Mesylate Nasal Solution—See PF Vol. 25 No. 6, page 9078.
Dimenhydrinate Injection—See PF Vol. 28 No. 3, page 752.
Dimenhydrinate Syrup—See PF Vol. 28 No. 3, page 755.
Dimenhydrinate Tablets—See PF Vol. 28 No. 3, page 756.
Dipryidamole Tablets—See PF Vol. 28 No. 5, page 1402.
Divalproex Sodium Delayed-Release Tablets—See PF Vol. 29 No. 3, page 625.
Dobutamine in Dextrose Injection—See PF Vol. 28 No. 5, page 1403.
Dolasetron Mesylate Injection—See PF Vol. 29 No. 1, page 60.
Doxazosin Mesylate—See PF Vol. 29 No. 1, page 61.
Doxazosin Tablets—See PF Vol. 29 No. 1, page 64.
Doxorubicin Hydrochloride—See PF Vol. 29 No. 1, page 66.
Egg Phospholipids—See PF Vol. 29 No. 2, page 401.
Ergoloid Mesylates Tablets—See PF Vol. 29 No. 3, page 626.
Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension—See PF Vol. 29 No. 3, page 626.
Estradiol Transdermal System—See PF Vol. 25 No. 6, page 9080.
Ethambutol Hydrochloride Tablets—See PF Vol. 28 No. 5, page 1406.
Ethosuximide Oral Solution—See PF Vol. 28 No. 5, page 1407.
Ethotoin—See PF Vol. 29 No. 1, page 66.
Ethylenediamine—See PF Vol. 28 No. 6, page 1789.
Etoposide—See PF Vol. 28 No. 5, page 1407.
Famotidine Tablets—See PF Vol. 29 No. 3, page 627.
Ferric Subsulfate Solution—See PF Vol. 28 No. 6, page 1789.
Ferric Sulfate—See PF Vol. 28 No. 6, page 1790.
Ferrous Fumarate—See PF Vol. 29 No. 3, page 629.
Ferrous Gluconate—See PF Vol. 29 No. 3, page 630.
Ferumoxides Injection—See PF Vol. 28 No. 3, page 758.
Fexofenadine Hydrochloride—See PF Vol. 28 No. 6, page 1790.
Fexofenadine Hydrochloride Capsules—See PF Vol. 28 No. 6, page 1793.

Finasteride Tablets—See PF Vol. 29 No. 2, page 403.
Flucytosine Capsules—See PF Vol. 29 No. 1, page 68.
Fludarabine Phosphate—See PF Vol. 28 No. 6, page 1795.
Fludarabine Phosphate for Injection—See PF Vol. 28 No. 6, page 1799.
Fluoxetine Hydrochloride—See PF Vol. 28 No. 6, page 1802.
Fluoxetine Tablets—See PF Vol. 28 No. 6, page 1803.
Fluoxetine Delayed-Release Capsules—See PF Vol. 29 No. 2, page 403.
Flutamide—See PF Vol. 29 No. 2, page 405.
Flutamide Capsules—See PF Vol. 29 No. 2, page 407.
Fluvastatin Capsules—See PF Vol. 25 No. 4, page 8423.
Folic Acid Tablets—See PF Vol. 29 No. 2, page 409.
Fosphenytoin Sodium Injection—See PF Vol. 29 No. 1, page 68.
Gabapentin—See PF Vol. 29 No. 1, page 72.
Gabapentin Capsules—See PF Vol. 28 No. 2, page 298.
Gadoversetamide—See PF Vol. 29 No. 2, page 410.
Gadoversetamide Injection—See PF Vol. 29 No. 2, page 415.
Ganciclovir—See PF Vol. 29 No. 3, page 630.
Ganciclovir for Injection—See PF Vol. 29 No. 3, page 630.
Gemcitabine Hydrochloride—See PF Vol. 27 No. 5, page 3141.
Gemcitabine for Injection—See PF Vol. 27 No. 5, page 3142.
Gemfibrozil—See PF Vol. 27 No. 6, page 3289.
Glipizide—See PF Vol. 29 No. 2, page 417.
Glyburide Tablets—See PF Vol. 29 No. 2, page 418.
Glycerin Injection—See PF Vol. 27 No. 5, page 3143.
Gonadorelin Hydrochloride—See PF Vol. 27 No. 3, page 2552.
Graftskin—See PF Vol. 28 No. 6, page 1804.
Heparin Sodium—See PF Vol. 29 No. 1, page 75.
0.1 Normal Hydrochloric Acid Intravenous Injection—See PF Vol. 27 No. 5, page 3144.
Hydrocodone Bitartrate—See PF Vol. 29 No. 3, page 630.
Hydrocodone Bitartrate and Acetaminophen Tablets—See PF Vol. 29 No. 3, page 633.
Hydrocodone Bitartate and Homatropine Methylbromide Tablets—See PF Vol. 28 No. 4, page 1267.
Ibuprofen Capsules—See PF Vol. 26 No. 2, page 360.
Indapamide Tablets—See PF Vol. 28 No. 5, page 1410.
Indinavir Sulfate—See PF Vol. 27 No. 2, page 2165.
Indinavir Sulfate Capsules—See PF Vol. 26 No. 6, page 1641.
Indium In 111 Ibritumomab Tiuxetan Injection—See PF Vol. 28 No. 6, page 1815.
Indocyanine Green—See PF Vol. 28 No. 3, page 765.
Indomethacin Topical Gel—See PF Vol. 24 No. 2, page 5808.
Inulin in Sodium Chloride Injection—See PF Vol. 28 No. 6, page 1817.
Iodixanol—See PF Vol. 29 No. 1, page 79.
Iodixanol Injection—See PF Vol. 29 No. 1, page 80.
Iodoform—See PF Vol. 28 No. 6, page 1817.
Irbesartan—See PF Vol. 24 No. 6, page 7156.
Irbesartan Tablets—See PF Vol. 24 No. 6, page 7157.
Irbesartan and Hydrochlorothiazide Tablets—See PF Vol. 24 No. 6, page 7158.
Isradipine Capsules—See PF Vol. 23 No. 4, page 4334.
Ivermectin—See PF Vol. 27 No. 1, page 1790.
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3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyl Tetrazolium Bromide—See PF Vol. 27 No. 6, page 3365.
Dioleoylglycerol—See PF Vol. 26 No. 6, page 1622.
1,2-Dioleoyl-3-linoleoyl-rac-glycerol—See PF Vol. 28 No. 3, page 849.
Disodium Arsenate—See PF Vol. 28 No. 4, page 1305.
Drabkin's Reagent—See PF Vol. 29 No. 2, page 507.
Escin—See PF Vol. 27 No. 4, page 2837.
17α-Estradiol—See PF Vol. 27 No. 2, page 2278.
Ethidium Bromide—See PF Vol. 27 No. 6, page 3366.
Ethylbenzene—See PF Vol. 28 No. 3, page 850.
Ferulic Acid—See PF Vol. 28 No. 6, page 1951.
9-Fluorenylmethyl Chloroformate—See PF Vol. 25 No. 5, page 8916.
Formamide, Anhydrous—See PF Vol. 27 No. 5, page 3115.
Glucose—See PF Vol. 28 No. 3, page 850.
L-Glutamic Acid—See PF Vol. 27 No. 6, page 3366.
L-Glutamine—See PF Vol. 27 No. 6, page 3366.
Guanidine Isothiocyanate—See PF Vol. 27 No. 6, page 3366.
Heptafluorobutyric Acid—See PF Vol. 26 No. 4, page 1132.
Hexadecane—See PF Vol. 28 No. 4, page 1305.
Hexadimethrine Bromide—See PF Vol. 29 No. 1, page 265.
Hexamethylenetetramine—See PF Vol. 28 No. 3, page 850.
L-Histidine Hydrochloride Monohydrate—See PF Vol. 27 No. 6, page 3366.
Homatropine Hydrobromide—See PF Vol. 28 No. 4, page 1305.
Hydrocodone Diol—See PF Vol. 28 No. 4, page 1306.
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Isoferulic Acid—See PF Vol. 27 No. 4, page 2837.
Isomaltotriose—See PF Vol. 28 No. 6, page 1952.
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Lanthanum Oxide—See PF Vol. 28 No. 3, page 851.
Lead Acetate Paper—See PF Vol. 29 No. 1, page 265.
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α-Lipoic Acid—See PF Vol. 27 No. 6, page 3367.
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3-Methyl-2-benzothiazolinone Hydrazone Hydrochloride—See PF Vol. 25 No. 3, page 8280.
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Nickel(II) Sulfate Heptahydrate—See PF Vol. 27 No. 5, page 3116.
Nitric Acid, Lead-Free—See PF Vol. 28 No. 3, page 851.
Nonylphenol Polyoxyethylene Ether—See PF Vol. 27 No. 6, page 3368.
Oligo-deoxythymidine—See PF Vol. 27 No. 6, page 3368.
Pentadecanoic Acid Methyl Ester—See PF Vol. 26 No. 6, page 1622.
o-Phenanthroline Monohydrochloride Monohydrate—See PF Vol. 27 No. 1, page 1904.
Phenol Red, Sodium—See PF Vol. 27 No. 6, page 3368.
Polyoxyethylene (23) Lauryl Ether—See PF Vol. 29 No. 2, page 507.
Polyoxyethylene (20) Sorbitan Monolaurate—See PF Vol. 27 No. 6, page 3368.
Protocatechuic Acid—See PF Vol. 28 No. 6, page 1952.
Putrescine Dihydrochloride—See PF Vol. 27 No. 6, page 3369.
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N-(2-Tetrahydrofuroyl)piperazine—See PF Vol. 25 No. 5, page 8748.
1,1,4,4-Tetraphenyl-1,3-butadiene—See PF Vol. 26 No. 6, page 1623.
Thymidine—See PF Vol. 27 No. 6, page 3369.
Trioleoylglycerol—See PF Vol. 26 No. 6, page 1623.
Tropine—See PF Vol. 28 No. 4, page 1306.
L-Tyrosine Disodium—See PF Vol. 27 No. 6, page 3370.
Vinyl Acetate—See PF Vol. 21 No. 2, page 466.
2-Vinylpyridine—See PF Vol. 26 No. 2, page 504.
1-Vinyl-2-pyrrolidone—See PF Vol. 22 No. 6, page 3249.
m-Xylene—See PF Vol. 28 No. 6, page 1952.
Zinc Sulfate Heptahydrate—See PF Vol. 26 No. 2, page 504.

Indicator Test Papers

Methyl Green—See PF Vol. 28 No. 4, page 1306.
Methyl Green—Iodomercurate Paper—See PF Vol. 28 No. 4, page 1306.
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Cupric Citrate TS—See PF Vol. 27 No. 5, page 3117.
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Perchloric Acid TS—See PF Vol. 27 No. 1, page 1905.

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Hydrochloric Acid, Alcoholic, Tenth-Molar (0.1 M)—See PF Vol. 28 No. 4, page 1235.
0.01 N Iodine VS—See PF Vol. 29 No. 3, page 812.
Potassium Hydroxide, Alcoholic, Tenth Molar (0.1 M)—See PF Vol. 28 No. 4, page 1235.
Tetrabutylammonium Hydroxide in Methanol/Isopropyl Alcohol, 0.1 N—See PF Vol. 29 No. 2, page 508.

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Footnote 85—See PF Vol. 26 No. 4, page 1133.
Footnote 87—See PF Vol. 26 No. 5, page 1383.
Footnote 99—See PF Vol. 27 No. 6, page 3374.
Footnote 100—See PF Vol. 27 No. 6, page 3374.
Footnote 101—See PF Vol. 27 No. 6, page 3374.
Footnote 102—See PF Vol. 27 No. 6, page 3374.
Footnote 103—See PF Vol. 28 No. 2, page 554.
Footnote 105—See PF Vol. 28 No. 6, page 1952.
Footnote 106—See PF Vol. 29 No. 1, page 266.
Footnote 107—See PF Vol. 29 No. 2, page 508.
Footnote 109—See PF Vol. 29 No. 2, page 508.

REFERENCE TABLES

Container Specifications for Capsules and Tablets—See PF Vol. 25 No. 5, page 8860; PF Vol. 25 No. 6, page 9176; PF Vol. 26 No. 1, page 145; PF Vol. 26 No. 3, page 836; PF Vol. 26 No. 4, page 1133; PF Vol. 26 No. 5, page 1384; PF Vol. 27 No. 1, page 1906; PF Vol. 27, No. 3, page 2597; PF Vol. 27 No. 5, page 3118; PF Vol. 28 No. 3, page 852; PF Vol. 28 No. 4, page 1235; PF Vol. 28 No. 6, page 1952; PF Vol. 29 No. 1, page 266; PF Vol. 29 No. 2, page 508.
Description and Relative Solubility of USP and NF Articles—See PF Vol. 23 No. 6, page 5310; PF Vol. 24 No. 5, page 7017; PF Vol. 25 No. 3, page 8282; PF Vol. 25 No. 4, page 8589; PF Vol. 25 No. 5, page 8917; PF Vol. 25 No. 6, page 9254; PF Vol. 26 No. 2, page 504 and 505; PF Vol. 26 No. 3, page 837; PF Vol. 26 No. 4, page 1135; PF Vol. 26 No. 5, page 1385; PF Vol. 27 No. 1, page 1907; PF Vol. 27 No. 2, page 2281; PF Vol. 27 No. 4, page 2839; PF Vol. 27 No. 5, page 3120; PF Vol. 27 No. 6, page 3374; PF Vol. 28 No. 2, page 554, PF Vol. 28 No. 3, page 853, PF Vol. 28 No. 4, page 1236, PF Vol. 28 No. 5, page 1542; PF Vol. 28 No. 6, page 1953; PF Vol. 29 No. 1, page 266; PF Vol. 29 No. 2, page 509; PF Vol. 29 No. 3, page 812.

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Chondroitin Sulfate Sodium—See PF Vol. 29 No. 2, page 456.
Chondroitin Sulfate Tablets—See PF Vol. 29 No. 3, page 692.
Black Cohosh—See PF Vol. 28 No. 5, page 1455.
Powdered Black Cohosh—See PF Vol. 28 No. 5, page 1460.
Powdered Black Cohosh Extract—See PF Vol. 28 No. 5, page 1461.
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Docosahexaenoic Acid—See PF Vol. 26 No. 6, page 1648.
Docosahexaenoic Acid Capsules—See PF Vol. 26 No. 6, page 1651.
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Eleuthero—See PF Vol. 26 No. 6, page 1596.
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Valerian Capsules—See PF Vol. 27 No. 1, page 1825.
Water-Soluble Vitamins with Minerals Capsules—See PF Vol. 28 No. 5, page 1547.
Water-Soluble Vitamins with Minerals Tablets—See PF Vol. 28 No. 5, page 1548.

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"Official" and "Official Articles"—See PF Vol. 28 No. 1, page 88.

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Ammonium Sulfate—See PF Vol. 29 No. 1, page 136.
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Candelilla Wax—See PF Vol. 29 No. 1, page 138.
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Carboxymethylcellulose Calcium—See PF Vol. 23 No. 6, page 5063.
Low-Substituted Carboxymethylcellulose Sodium—See PF Vol. 28 No. 5, page 1617.
Carboxymethylcellulose Sodium Suspension—See PF Vol. 25 No. 3, page 8088.
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Vitamin E Polyethylene Glycol Succinate—See PF Vol. 28 No. 6, page 1909.
Polyisobutylene—See PF Vol. 29 No. 1, page 150.
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Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled

(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)

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Cabergoline Tablets (new)	24	6	7142
Carbon Dioxide—*Air*, *Assay*	28	4	1082
Carboxymethylcellulose Sodium (new)	26	5	1403
†Cefuroxime Axetil Tablets—*Dissolution Test 2*	27	2	2128
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Enalaprilat Injection (new)	19	4	5587
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Enoxaparin Sodium Injection (new)	22	6	3038
Epinephryl Borate Ophthalmic Solution—*USP Reference standards*, *Assay*	23	3	3991
Fluoxetine Capsules—*Chromatographic purity*, *Related compounds*, *Assay*	27	2	2150
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†Ketamine Hydrochloride—*Assay*	28	4	1140
Mecamylamine Hydrochloride (entire submission)	28	2	320
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Methylcellulose—*Harmonization* (new)	24	5	6737
Montelukast Sodium (new)	24	6	7160
Montelukast Sodium Tablets (new)	24	6	7162
Morphine Sulfate Extended-Release Capsules (new)	25	4	8426
Oxybutynin Chloride—*Chromatographic purity*	26	6	1561
Perflutren Protein-Type A Microspheres for Injection [Former title: Albumin Encapsulated Octafluoropropane Microspheres for Injection] (new)	27	4	2769
Povidone (entire submission)	22	6	3163
Sertraline Hydrochloride (new)	24	6	7179
Sertraline Hydrochloride Tablets (new)	24	6	7181
Sulindac—*Chromatographic purity*	25	5	8879
Sulindac Tablets	25	5	8880
Sunflower Oil—*Briefing*	27	4	2779
Titanium Dioxide (new)	24	2	5796
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Sterile Vancomycin Hydrochloride—*Title*	27	4	2786
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USP Povidone RS	20	5	8060
USP Sulindac Related Compound A RS	25	5	8893
†⟨71⟩ Sterility Tests (entire submission)	26	4	1102
⟨661⟩ Containers—*Polypropylene Containers* (added)	26	4	1117
⟨786⟩ Particle Size Distribution Estimation by Analytical Sieving—*Harmonization*	25	1	7460
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†⟨1186⟩ Shipping and Storage of Labile Preparations	28	2	495
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Benzyl Alcohol (entire submissions)	27	4	2790, 2855
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Hydroxyethyl Cellulose (entire submission)	20	6	8311
Hydroxypropyl Beta Cyclodextrin (new)	24	6	7284
Silicon Dioxide (entire submission)	24	6	7191
Colloidal Silicon Dioxide—*Harmonization*	24	6	7187, 7194
Sodium Starch Glycolate (entire submission)	22	6	3202
Rice Starch (new)	23	4	4348
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2-Isopropylphenol (new)	27	4	2838
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†Footnote 108	29	2	508

†New cancellations in 29(4).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

MONOGRAPHS (NF)

BRIEFING

Microcrystalline Cellulose, *NF 21* page 2713. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for the subject article. The revisions presented in this proposal, which represents the revised OFFICIAL INQUIRY STAGE 4 draft in the harmonization process, reflect those changes suggested by EP and JP. Because of significant changes within the CONSENSUS STAGE 5B draft, the draft has been reverted back to the OFFICIAL INQUIRY STAGE 4. Readers are urged to review these *In-Process Revision* proposals carefully and to respond to USP no later than August 31, 2003.

Major changes from the current *NF* monograph include the following:

(1) Definition—No change.
(2) *Packaging and storage*—Storage conditions are added.
(3) *Labeling*—No change.
(4) *Identification* test *B*—This test is deleted. The former test *C* is now labeled as test *B*. The deleted test is considered a functionality test, which is not appropriate for Harmonization.
(5) *Microbial limits*—No change.
(6) *Conductivity*—No change.
(7) *pH*—The upper limit is increased to 7.5 from 7.0 to conform to EP and JP standards and to be consistent with the monograph for *Powdered Cellulose*.
(8) *Loss on drying*—No change.
(9) *Residue on ignition*—The standard for this test was increased to not more than 0.1%, which conforms to EP standards.
(10) *Bulk density*—No change.
(11) *Water-soluble substances*—The standard for this test was changed from 0.24% to 0.25%.
(12) *Ether-soluble substances*—No change.
(13) *Heavy metals*—No change.
(14) *Organic volatile impurities*—No change.

(EMC: J. Lane) RTS—39840-1

Change to read:

Microcrystalline Cellulose

Cellulose.

Cellulose [*9004-34-6*].

» Microcrystalline Cellulose is purified, partially depolymerized cellulose prepared by treating alpha cellulose, obtained as a pulp from fibrous plant material, with mineral acids.

Packaging and storage—Preserve in tight containers at room temperature.

Labeling—The labeling indicates the nominal loss on drying, bulk density, and degree of polymerization values. Degree of polymerization compliance is determined using *Identification* test *B*. Where the particle size distribution is stated in the labeling, the labeling indicates the d_{10}, d_{50}, and d_{90} values and the range for each.

Identification—

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Microcrystalline Cellulose on a watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.

B: Transfer 1.3 g of Microcrystalline Cellulose, accurately weighed to 0.1 mg, to a 125-mL conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanical shaker until completely dissolved. Transfer 7.0 mL of the solution to a calibrated number 150 Cannon-Fenske or equivalent[1] viscosimeter. Allow the solution to equilibrate at 25 $\pm$ 0.1° for not less than 5 minutes. Time the flow between the 2 marks on the viscosimeter, and record the flow time, t_1, in seconds. Calculate the kinematic viscosity, $(KV)_1$, of the Microcrystalline Cellulose taken by the formula:

$$t_1(k_1),$$

[1] A Ubbelohde 1C viscosimeter is equivalent to a Cannon-Fenske 150 viscosimeter. A Ubbelohde 1 viscosimeter is equivalent to a Cannon-Fenske 100 viscosimeter.

in which k_1 is the viscosimeter constant (see *Viscosity* ⟨911⟩). Obtain the flow time, t_2, for a 0.5 M cupriethylenediamine hydroxide solution using a number 100 Cannon-Fenske or equivalent[1] viscosimeter. Calculate the kinematic viscosity, $(KV)_2$, of the solvent by the formula:

$$t_2(k_2),$$

in which k_2 is the viscosimeter constant. Determine the relative viscosity, η_{rel}, of the Microcrystalline Cellulose specimen taken by the formula:

$$(KV)_1 / (KV)_2.$$

Determine the intrinsic viscosity, $[\eta]c$, by interpolation, using the *Intrinsic Viscosity Table* in the *Reference Tables* section. Calculate the degree of polymerization, *P*, by the formula:

$$(95)[\eta]c / W_S[(100 - \%LOD)/100],$$

in which W_S is the weight, in g, of the Microcrystalline Cellulose taken, and % *LOD* is the value obtained from the test for *Loss on drying.* The degree of polymerization is not greater than 350, and is within the labeled specification.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 per g, the total combined molds and yeasts count does not exceed 100 per g, and it meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and for absence of *Escherichia coli* and *Salmonella* species.

Conductivity—Shake about 5 g with 40 mL of water for 20 minutes, and centrifuge. Retain the supernatant liquid for use in the *pH* test. Using an appropriate conductivity meter that has been standardized with a potassium chloride conductivity calibration standard[2] having a conductivity of 100 µS per cm, measure the conductivity of the supernatant solution after a stable reading is obtained, and measure the conductivity of the water used to prepare the test specimen. The conductivity of the supernatant solution does not exceed the conductivity of the water by more than 75 µS per cm.

pH ⟨791⟩: between 5.0 and 7.5 in the supernatant solution obtained in the *Conductivity* test.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 7.0% of its weight, or some other lower percentage, or is within a percentage range, as specified in the labeling.

Residue on ignition ⟨281⟩: not more than 0.1%. Ignition temperature 600 ± 50°.

Bulk density—Use a volume meter[3] that has been fitted with a 10-mesh screen. The volume meter is freestanding of the brass or stainless steel cup, which is calibrated to a capacity of 25.0 ± 0.05 mL and has an inside diameter of 30.0 ± 2.0 mm. Weigh the empty cup, position it under the chute, and slowly pour the powder from a height of 5.1 cm (2 inches) above the funnel through the volume meter, at a rate suitable to prevent clogging, until the cup overflows. [NOTE—If excessive clogging of the screen occurs, remove

[2] Commercially available conductivity calibration solutions for conductivity meter standardization, standardized by methods traceable to the National Institute of Science and Technology (NIST), may be used. Solutions prepared according to instructions given in ASTM Standard D1125 may be used provided the conductivity of the resultant solution is the same as that of the solution prepared from the NIST-certified material.

[3] A suitable apparatus is described as the Scott Volumeter in ASTM B 329, available from the American Society for Testing and Materials, 100 Barr Harbor Drive, West Conshohocken, PA 19429-2959.

the screen.] Level the excess powder, and weigh the filled cup. Calculate the bulk density by dividing the weight of the powder in the cup by the volume of the cup: the bulk density is within the labeled specification.

Water-soluble substances—Shake 5.0 g with about 80 mL of water for 10 minutes, filter with the aid of vacuum through filter paper (Whatman No. 42 or equivalent) into a vacuum flask. Transfer the filtrate to a tared beaker, evaporate to dryness without charring, dry at 105° for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 12.5 mg (0.25%).

Ether-soluble substances—Place 10.0 g in a chromatography column having an internal diameter of about 20 mm, and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the residue at 105° for 30 minutes, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 5.0 mg (0.05%).

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

BRIEFING

Powdered Cellulose, *NF 21* page 2714. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of compendial standards for the subject article. The revisions presented in this proposal, which represents the revised OFFICIAL INQUIRY STAGE 4 draft in the harmonization process, reflect those changes suggested by EP and JP. Because of significant changes within the CONSENSUS STAGE 5B draft, the draft has been reverted back to the OFFICIAL INQUIRY STAGE 4. Readers are urged to review these *In-Process Revision* proposals carefully and to respond to USP no later than July 31, 2003.

Major changes from the current *NF* monograph include the following:

(1) Definition—No change.
(2) *Packaging and storage*—Storage conditions are added.
(3) *Labeling*—No change.
(4) *Identification* test *B*—This test is deleted. The former test *C* is now labeled as test *B*. The deleted test is considered a functionality test, which is not appropriate for Harmonization.
(5) *Microbial limits*—No change.
(6) *pH*—No change.
(7) *Loss on drying*—The limit is increased to 6.5% from 6.0% to conform to EP and JP standards. The drying time is increased to 3 hours from 2 hours.
(8) *Residue on ignition*—No change.
(9) *Water-soluble substances*—No change.
(10) *Ether-soluble substances*—No change.
(11) *Heavy metals*—No change.
(12) *Organic volatile impurities*—No change.

(EMC: J. Lane) RTS—39840-2

Change to read:

Powdered Cellulose

» Powdered Cellulose is purified, mechanically disintegrated cellulose prepared by processing alpha cellulose obtained as a pulp from fibrous plant materials.

Packaging and storage—Preserve in tight containers at room temperature.

Labeling—The labeling indicates the nominal degree of polymerization value. Degree of polymerization compliance is determined using *Identification* test *B*.

Identification—

A: Prepare iodinated zinc chloride solution by dissolving 20 g of zinc chloride and 6.5 g of potassium iodide in 10.5 mL of water. Add 0.5 g of iodine, and shake for 15 minutes. Place about 10 mg of Powdered Cellulose on a watch glass, and disperse in 2 mL of iodinated zinc chloride solution: the substance takes on a violet-blue color.

B: Transfer 0.25 g of Powdered Cellulose, accurately weighed to 0.1 mg, to a 125-mL conical flask. Add 25.0 mL of water and 25.0 mL of 1.0 M cupriethylenediamine hydroxide solution. Immediately purge the solution with nitrogen, insert the stopper, and shake on a wrist action shaker or other suitable mechanical shaker until completely dissolved. Transfer 7.0 mL of the solution to a calibrated number 150 Cannon-Fenske or equivalent[1] viscosimeter. Allow the solution to equilibrate at 25 ± 0.1° for not less than 5 minutes. Time the flow between the 2 marks on the viscosimeter, and record the flow time, t_1, in seconds. Calculate the kinematic viscosity, $(KV)_1$, of the Powdered Cellulose taken by the formula:

$$t_1\ (k_1),$$

in which k_1 is the viscosimeter constant (see *Viscosity* ⟨911⟩). Obtain the flow time, t_2, for a 0.5 M cupriethylenediamine hydroxide solution using a number 100 Cannon-Fenske or equivalent[1] viscosimeter. Calculate the kinematic viscosity, $(KV)_2$, of the solvent by the formula:

$$t_2\ (k_2),$$

in which k_2 is the viscosimeter constant. Determine the relative viscosity, η_{rel}, of the Powdered Cellulose specimen taken by the formula:

$$(KV)_1 / (KV)_2.$$

Determine the intrinsic viscosity, $[\eta]c$, by interpolation, using the *Intrinsic Viscosity Table* in the *Reference Tables* section. Calculate the degree of polymerization, *P*, by the formula:

$$(95)[\eta]c / W_S[(100 - \%LOD)/100],$$

in which W_S is the weight, in g, of the Powdered Cellulose taken, and %*LOD* is the value obtained from the test for *Loss on drying*. The degree of polymerization is between 440 and 2250 and is within the labeled specification.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 1000 per g, the total combined molds and yeasts count does not exceed 100 per g, and it meets the requirements of the tests for absence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* and for absence of *Escherichia coli* and *Salmonella* species.

pH ⟨791⟩—Mix 10 g with 90 mL of water, and allow to stand with occasional stirring for 1 hour: the pH of the supernatant liquid is between 5.0 and 7.5.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 6.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.3%, calculated on the dried basis, the addition of sulfuric acid being omitted from the procedure. Ignition temperature of 600 ± 50°.

Water-soluble substances—Mix 6.0 g with 90 mL of recently boiled and cooled water, and allow to stand with occasional stirring for 10 minutes. Filter, with the aid of vacuum, discard the first 10 mL of the filtrate, and pass the filtrate through the same filter a second time, if necessary, to obtain a clear filtrate. Evaporate a 15.0-mL portion of the filtrate in a tared evaporating dish to dryness without charring, dry at 105° for 1 hour, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 15.0 mg (1.5%).

Ether-soluble substances—Place 10.0 g in a chromatography column having an internal diameter of about 20 mm, and pass 50 mL of peroxide-free ether through the column. Evaporate the eluate to dryness in a previously dried and tared evaporating dish with the aid of a current of air in a fume hood. After all the ether has evaporated, dry the resi-

[1] A Ubbelohde 1C viscosimeter is equivalent to a Cannon-Fenske 150 viscosimeter. A Ubbelohde 1 viscosimeter is equivalent to a Cannon-Fenske 100 viscosimeter.

due at 105° for 30 minutes, cool in a desiccator, and weigh: the difference between the weight of the residue and the weight obtained from a blank determination does not exceed 15.0 mg (0.15%).

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

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

BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How To Use PF*), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:

(PA5: K. Russo) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

MONOGRAPHS (NF)

BRIEFING

Polyethylene Glycol, *NF 21* page 2810, page 382 of the *Addendum to the First Interim Revision Announcement to USP 26–NF 21* in *PF* 29(2) [Mar.–Apr. 2003], and page 702 of *PF* 29(3) [May–June 2003]. The following revisions are an effort to update the current *NF* monograph. Most of the changes are intiated by proposed changes within the international harmonization process. Major changes proposed include the following:

(1) Definition—The limits for the average molecular weight have been deleted from the monograph. This was considered redundant when viscosity is tested and limited.
(2) *Packaging and storage*—Well-closed containers has been changed to tight containers, due to the potential volatility of some low molecular weight polyethylene glycols that are in liquid form.
(3) *Labeling*—Allowance and labeling for blends of polyethylene glycols are added.
(4) *USP Reference standards*—Two new reference standards are added to comply with the proposed IR test.
(5) *Completeness and color of solution*—A numerical limit specification for color is added to reduce the subjectivity of the current *Completeness and color of solution* test.
(6) *Identification*—The addition of a new, definitive *Identification* test based on IR spectroscopy performed by comparison with two reference substances: one of low molecular weight (300), and one of high molecular weight (8000). The test for *Viscosity* was also moved to the *Identification* section, because it can be used to distinguish between the various types of materials.
(7) *Viscosity*—A new method for *Viscosity* has been proposed, as it is easier to perform and complies to the range of 200 to 35,000 molecular weight. The temperature is changed from 98.9 ± 0.3° to 20 ± 3°. *Viscosity* was moved and is now under *Identification*.
(8) *Average molecular weight*—This test is deleted, based on the viscosity-molecular weight relationship among the polyethylene glycols.
(9) *pH*—The limit is changed from between 4.5 and 7.5 to 4.0 and 7.5.
(10) *Residue on ignition*—A sample weight of 10g is proposed, which is sufficient for a limit of not more than 0.1%.
(11) *Heavy metals*—This test has been deleted because polyethylene glycol is totally organic and not derived from any materials that usually contain heavy metals.
(12) *Limit of free ethylene oxide and 1,4-dioxane*—No change.
(13) *Limit of ethylene glycol and diethylene glycol*—A proposed capillary gas chromatographic method for the *Limit of ethylene glycol and diethylene glycol* test and a reduced limit based on the current limit in the *U.S. Code of Federal Regulations*. The limit was changed to not more than 620 ppm for ethylene glycol to comply with current International Conference on Harmonization (ICH) guidelines.
(14) *Water*—A new test for *Water* is added, with a limit corresponding to that in the *JP* monograph test.
(15) *Formaldehyde limit*—This test is added to reduce cross-linking, when polyethylene glycol is used with gelatin capsules.
(16) *Organic volatile impurities*—This test has been deleted because it is unnecessary for this compound.

(EMC: J. Lane) RTS—39925-1

Delete the following:
~~Pharmacy Equivalent Name: PEG~~

Change to read:

» Polyethylene Glycol is an addition polymer of ethylene oxide and water, represented by the formula:

$$H(OCH_2CH_2)_nOH,$$

in which *n* represents the average number of oxyethylene groups. ~~The average molecular weight is not less than 95.0 percent and not more than 105.0 percent of the labeled nominal value if the labeled nominal value is below 1000; it is not less than 90.0 percent and not more than 110.0 percent of the labeled nominal value if the labeled nominal value is between 1000 and 7000; it is not less than 87.5 percent and not more than 112.5 percent of the labeled nominal value if the labeled nominal value is above 7000.~~

The nominal average molecular weight is from 200 to 35,000. For blends of two or more discrete Polyethylene Glycols, each Polyethylene Glycol component of the blend must meet the monograph requirements for its nominal average molecular weight, and the blend must meet all other monograph requirements, except for viscosity. •It may contain a suitable antioxidant.•1

Change to read:
Packaging and storage—Preserve in tight containers,

away from direct sunlight. [Appropriate storage conditions to come.]

Change to read:

Labeling—Label it to state, as part of the official title, the average nominal molecular weight of the Polyethylene Glycol.

Blends of two or more discrete Polyethylene Glycols must be labeled to state, as part of the official title, the word "blend."

•Label it to indicate the name and quantity of any added antioxidant.•1

Add the following:

USP Reference standards ⟨11⟩—*USP Polyethylene Glycol 300 RS. USP Polyethylene Glycol 8000 RS.*

Change to read:

Completeness and color of solution—~~A solution of 5 g of Polyethylene Glycol in 50 mL of water is colorless; it is clear for liquid grades and not more than slightly hazy for solid grades.~~

Dissolve 5 g of Polyethylene Glycol in 50 mL of water. The color of the solution is not greater than 25 Pt-Co, and at 25 ± 5° the solution is clear for nominal molecular weights less than or equal to 1000 and not more than slightly hazy for nominal molecular weights greater than 1000.

Add the following:

Identification—

A: *Infrared Absorption* ⟨197F⟩—Use a thin film of test specimen, melt if necessary, on undried specimen, in the range from 4000 cm^{-1} to 600 cm^{-1}.

B: It complies with the test for *Viscosity.*

Change to read:

Viscosity ⟨911⟩—Determine its

kinematic

viscosity, using a capillary viscosimeter giving a flow time of not less than 200 seconds, and a liquid bath maintained at ~~98.9 ± 0.3° C (210° F)~~ 20 ± 3°. For Polyethylene Gycols having a relative molecular weight greater than 400, determine the viscosity on a 50% w/w solution of the substance to be examined.

The viscosity is within the limits specified in the accompanying table. For a Polyethylene Glycol not listed in the table, calculate the limits by interpolation.

Nominal Average Molecular Weight	Kinematic Viscosity Range, Centistokes ($mm^2 \cdot s^{-1}$)
200	53–62
300	71–94
400	94–116
600	13.9–18.5
1000	20.4–27.7
1500	31–46
3000	69–93
3350	76–110
4000	102–158
6000	185–250
8000	240–472
10,000	500–675
12,000	1000–1300
20,000	2500–3200
35,000	10,000–13,000

Delete the following:

~~**Average molecular weight**~~

~~*Phthalic anhydride solution*—Place 49.0 g of phthalic anhydride into an amber bottle, and dissolve in 300 mL of pyridine from a freshly opened bottle or that has been freshly distilled over phthalic anhydride. Shake vigorously until completely dissolved. Add 7 g of imidazole, swirl carefully to dissolve, and allow to stand for 16 hours before using.~~

~~*Test preparation for liquid Polyethylene Glycols*—Carefully introduce 25.0 mL of the *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an accurately weighed amount of the specimen, equivalent to its expected average molecular weight divided by 160. Insert the stopper in the bottle, and wrap it securely in a cloth bag.~~

~~*Test preparation for solid Polyethylene Glycols*—Carefully introduce 25.0 mL of *Phthalic anhydride solution* into a dry, heat-resistant pressure bottle. Add an accurately weighed amount of the specimen, equivalent to its expected molecular weight divided by 160; however, because of limited solubility, do not use more than 25 g. Add 25 mL of pyridine, from a freshly opened bottle or that has been freshly distilled over phthalic anhydride, swirl to dissolve, insert the stopper in the bottle, and wrap it securely in a cloth bag.~~

~~*Procedure*—Immerse the bottle in a water bath maintained at a temperature between 96° and 100°, to the same depth as that of the mixture in the bottle. Remove the bottles from the bath after 5 minutes, and, without unwrapping, swirl for 30 seconds to homogenize. Heat in the water bath for 30 minutes (60 minutes for Polyethylene Glycols having molecular weights of 3000 or higher), then remove from the bath, and allow it to cool to room temperature. Uncap the bottle carefully to release any pressure, remove from the bag, add 10 mL of water, and swirl thoroughly. Wait 2 minutes, add 0.5 mL of a solution of phenolphthalein in pyridine (1 in 100), and titrate with 0.5 N sodium hydroxide VS to the first pink color that persists for 15 seconds, recording the volume, in mL, of 0.5 N sodium hydroxide required as *S*. Perform a blank determination on 25.0 mL of *Phthalic anhydride solution* plus any additional pyridine added to the bottle, and record the volume, in mL, of 0.5 N sodium hydroxide required as *B*. Calculate the average molecular weight by the formula:~~

$$~~[2000W]/[(B - S)(N)],~~$$

~~in which *W* is the weight, in g, of the Polyethylene Glycol taken for the *Test preparation*, $(B - S)$ is the difference between the volumes of 0.5 N sodium hydroxide consumed by the blank and by the specimen, and *N* is the normality of the sodium hydroxide solution.~~

Change to read:

pH ⟨791⟩: ~~between 4.5 and 7.5, determined potentiometrically, in a solution prepared by dissolving 5.0 g of Polyethylene Glycol in 100 mL of carbon dioxide–free water and adding 0.30 mL of saturated potassium chloride solution.~~

Dissolve 5.0 g of Polyethylene Glycol in 100 mL of water with an unadjusted pH of 5.0 or greater, stirring in a sealed bottle, if necessary. To this solution, add 0.30 mL of a saturated solution of potassium chloride. The test solution should be maintained at 25 ± 2° during the measurement. The measured pH is between 4.0 and 7.5.

Add the following:

Water, *Method Ia* ⟨921⟩: not more than 1.0%.

Change to read:

Residue on ignition ⟨281⟩: not more than 0.1%, a ~~25-g~~

10-g

specimen and a tared platinum dish being used, and the residue being moistened with 2 mL of sulfuric acid.

Delete the following:

~~**Heavy metals** ⟨231⟩—Mix 4.0 g with 5.0 mL of 0.1 N hydrochloric acid, and dilute with water to 25 mL: the limit is 5 ppm.~~

Delete the following:

~~**Limit of ethylene glycol and diethylene glycol** (for Polyethylene Glycol having a nominal molecular weight less than 450)—~~

~~*Standard preparation*—Prepare an aqueous solution containing 500 µg each of ethylene glycol and of diethylene glycol per mL.~~

~~*Test preparation*—Transfer about 4 g of Polyethylene Glycol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with water to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 1.5-m stainless steel column packed with 12% G13 on support S1NS. The carrier gas is nitrogen or another suitable inert gas, flowing at a rate of 50 mL per minute. The column temperature is maintained at about 140°, the injection port temperature is maintained at about 250°, and the flame-ionization detector temperature is maintained at 280°.~~

~~*Procedure*—Inject a volume (about 2.0 µL) of the *Standard preparation* into the chromatograph, and record the chromatogram, adjusting the operational conditions to obtain peaks not less than 10 cm in height. Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as P_1 and P_2, respectively. Inject a volume (about 2.0 µL) of the *Test preparation* into the chromatograph, and record the chromatogram under the same conditions as those employed for the *Standard preparation*. Measure the heights of the first (ethylene glycol) and second (diethylene glycol) peaks, and record the values as p_1 and p_2, respectively. Calculate the percentage of ethylene glycol in the portion of Polyethylene Glycol taken by the formula:~~

~~$$(C_1p_1)/(P_1W),$$~~

~~in which C_1 is the concentration, in µg per mL, of ethylene glycol in the *Standard preparation;* and W is the weight, in mg, of Polyethylene Glycol taken. Calculate the percentage of diethylene glycol in the portion of Polyethylene Glycol taken by the formula:~~

~~$$(C_2p_2)/(P_2W),$$~~

~~in which C_2 is the concentration, in µg per mL, of diethylene glycol in the *Standard preparation:* not more than 0.25% of the sum of ethylene glycol and diethylene glycol is found.~~

Delete the following:

~~**Limit of ethylene glycol and diethylene glycol** (for Polyethylene Glycol having a nominal molecular weight 450 or above but not more than 1000)—~~

~~*Ceric ammonium nitrate solution*—Dissolve 6.25 g of ceric ammonium nitrate in 100 mL of 0.25 N nitric acid. Use within 3 days.~~

~~*Standard preparation*—Transfer 62.5 mg of diethylene glycol to a 25-mL volumetric flask, dissolve in a mixture of equal volumes of freshly distilled acetonitrile and water, dilute with the same mixture to volume, and mix.~~

~~*Test preparation*—Dissolve 50.0 g of Polyethylene Glycol in 75 mL of diphenyl ether, previously warmed, if necessary, just to melt the crystals, in a 250-mL distilling flask. Slowly distil at a pressure of 1 mm to 2 mm of mercury, into a receiver graduated to 100 mL in 1-mL subdivisions, until 25 mL of distillate has been collected. Add 20.0 mL of water to the distillate, shake vigorously, and allow the layers to separate. Cool in an ice bath to solidify the diphenyl ether and facilitate its removal. Filter the separated aqueous layer, wash the diphenyl ether with 5.0 mL of ice-cold water, pass the washings through the filter, and collect the filtrate and washings in a 25-mL volumetric flask. Warm to room temperature, dilute with water to volume, if necessary, and mix. Mix this solution with 25.0 mL of freshly distilled acetonitrile in a glass-stoppered, 125-mL conical flask.~~

~~*Procedure*—Transfer 10.0 mL each of the *Standard preparation* and the *Test preparation* to separate 50-mL flasks, each containing 15.0 mL of *Ceric ammonium nitrate solution*, and mix. Within 2 to 5 minutes, concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 450 nm, with a suitable spectrophotometer, using a blank consisting of a mixture of 15.0 mL of *Ceric ammonium nitrate solution* and 10.0 mL of a mixture of equal volumes of freshly distilled acetonitrile and water: the absorbance of the solution from the *Test preparation* does not exceed that of the solution from the *Standard preparation*, corresponding to not more than 0.25% of combined ethylene glycol and diethylene glycol.~~

Add the following:

Limit of ethylene glycol and diethylene glycol—

NOTE—Applies to Polyethylene Glycol having a nominal molecular weight of 200 or above but not more than 1000; testing not required for nominal molecular weights greater than 1000.

Internal standard solution—Prepare a solution in water containing about 1000 µg of 1,4-butanediol in each mL.

Standard solution—Prepare a solution in water containing about 500 µg of ethylene glycol, about 500 µg of diethylene glycol, and about 500 µg of 1,4-butanediol in each mL.

Test solution—Transfer about 4 g of Polyethylene Glycol, accurately weighed, to a small bottle. Pipet 5 mL of *Internal standard solution* and 1 mL of water into the bottle. Cap the bottle, and shake to mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a split injection system, and a 0.53-mm × 30-m fused-silica analytical column coated with 1.2-µm film of phase G16 (or, preferably, its bonded equivalent). The carrier gas is helium, flowing at a rate of about 40 cm per second, and the split vent flow is about 100 mL per minute. The injection port and detector temperatures are maintained at 250° and 260°, respectively. The column temperature is programmed to increase from 180° to 260° at a rate of 10° per minute, and then it is maintained at 260° for at least 22 minutes.

Procedure—Inject 1 µL of the *Standard solution* into the chromatograph, record the chromatogram, and record the areas of the first (ethylene glycol), the second (internal standard), and third (diethylene glycol) peaks as r_{SE}, r_{SI}, and r_{SD}, respectively. Inject 1 µL of the *Test solution* into the chromatograph, and record the chromatogram as directed for *Standard solution*. Use the retention times observed in the chromatogram of the *Standard solution* to identify the peaks in the chromatogram of the *Test solution* corresponding to ethylene glycol, the internal standard, and diethylene glycol. Record the areas of the ethylene glycol, the internal standard, and diethylene glycol peaks as r_E, r_I, and r_D, respectively. Calculate the response factors, F_N, of ethylene glycol and diethylene glycol by the formula:

$$(C_N r_{SI}) / (C_{SI} r_{SN}),$$

in which C_N is the concentration, in µg per mL, of the analyte of interest in the *Standard solution*; r_{SI} is the peak area for the internal standard obtained from the *Standard solution*; C_{SI} is the concentration, in µg per mL, of the internal standard in the *Standard solution*; and r_{SN} is the peak area for the analyte of interest obtained from the *Standard solution*. Calculate the percentages, by weight, of ethylene glycol and diethylene glycol in the portion of Polyethylene Glycol taken by the formula:

$$(F_N C_I r_N) / (2000 r_I W),$$

in which F_N is as obtained above; C_I is the concentration, in µg per mL, of the internal standard in the *Internal standard solution*; r_N and r_I are the peak areas of the analyte of interest and the internal standard, respectively, obtained from the *Test solution*; and W is the weight, in g, of Polyethylene Glycol in the *Test solution*: not more than 620 ppm ethylene glycol and not more than 0.2% of ethylene glycol and diethylene glycol combined is found.

Add the following:

Limit of formaldehyde—

Chromotropic acid sodium solution—Dissolve 0.60 g of chromotropic acid disodium salt in about 80 mL of water, and dilute with water to 100 mL. [NOTE—Use this solution within 24 hours.]

Test solution—To 1.0 g, add 5.0 mL of *Chromotropic acid sodium solution,* and cool in iced water. Allow to stand for 15 minutes; and dilute slowly with water to 10 mL.

Reference solution—Dilute 0.860 g of formaldehyde solution to 100 mL with water. Dilute 1.0 mL of this solution to 100 mL with water. In a 10 mL flask, mix 1.00 mL of this solution with 5.0 mL of *Chromotropic acid sodium solution,* cool in iced water. Allow to stand for 15 minutes, and dilute slowly with water to 10 mL.

Blank solution—In a 10-mL flask mix 1.00 mL of water with 5.0 mL of *Chromotropic acid sodium solution*, and cool in iced water. Dilute slowly with water to 10 mL. Determine at 567 nm against the *Blank solution*, that the absorbance of the *Test solution* is not higher than that of the *Reference solution* (0.003%).

Delete the following:

~~**Organic volatile impurities,** *Method IV* ⟨467⟩: meets the requirements for chloroform, methylene chloride, and trichloroethylene.~~

DIETARY SUPPLEMENTS MONOGRAPHS

BRIEFING

Pygeum; Pygeum Extract; Pygeum Capsules. Because there are no existing *USP* monographs for these botanicals, new monographs are being previewed.

(DSB: G. Giancaspro) RTS—37249-1

Add the following:

Pygeum

» Pygeum consists of the bark of *Prunus africana* (Hook f.) Kalkman (*Pygeum africanum* Hook f.) Rosaceae. It contains not less than 9.0 percent of extractable matters.

Packaging and storage—Preserve in well-closed containers, and store at room temperature.

Labeling—The label states the Latin binomial and, following the official name, the parts of the plant contained in the article.

USP Reference standards ⟨11⟩—*USP Pygeum Extract RS*. *USP* β-*Sitosterol RS*.

Botanic characteristics—

Macroscopic—Bark pieces consist of long fragments of variable dimensions, from only a few cm to 1-m long with a thickness varying from a few mm to 1–2 cm. The color is brown, more or less dark on the external surface; light brown to red brown on the internal surface. The external part of the bark presents a very dark and fissured rhytidome that in the samples of old trees is fragmented in more or less square plaques of about 1 to 5 cm. The thickness varies from 1 mm in young plants or branches to 5–8 mm in old plants. The outer surface may also be covered with whitish lichens or thin filamentous moss. The internal bark, under the rhytidome, is clearer and has a more reddish coloration, with a long fibrous break, from reddish to light brown and dark brown in color, often presenting concentrical stratification cracks. The internal surface is more clear and presents small wrinkles.

Microscopic—The transverse section of the bark presents a suberized bed having a thickness depending on the age of the plant, consisting of multiple layers of small, square cells with the walls of moderate thickness. It presents a cortical parenchyma of more or less round cells, with a few apparent formations of very thin-walled sclerites, definitely sharp. Often, in the parenchyma, there are groups of cells containing oxalate druses; a few bigger cells with highly thickened walls can also be observed. It shows a liber with phloem zones and presenting medulary rays. The phloemical portions contain groups of fibrous cells with highly thickened

walls as well as phloemical and parenchymal elements sometimes containing druses of oxalate. The medulary rays are of conical shape, larger on the external surface and thinner on the internal side; they can also contain druses of oxalate.

Thin-layer chromatographic identification test ⟨201⟩—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Transfer about 10 g of the powdered plant material to a soxhlet apparatus. Extract with 150 mL of methylene chloride for 4 hours. Evaporate the extract under vacuum to dryness. Dissolve the residue with 10 mL of methylene chloride. Apply 10 µL to the plate.

Standard solution 1—Prepare a solution of USP Pygeum Extract RS in chloroform having a concentration of about 10 mg per mL.

Standard solution 2—Prepare a solution of USP β-Sitosterol RS in chloroform having a concentration of about 1 mg per mL.

Developing solvent system: methylene chloride in a saturated chamber.

Spray reagent—Prepare a solution of sulfuric acid and water (1:1).

Procedure—Develop the chromatogram to a length of not less than 15 cm, and dry the plate in a current of air. Spray the plate with *Spray reagent*, and heat the plate at 100° for 10 minutes. Examine the plate under white light: the chromatogram obtained with the *Test solution* shows one red-violet zone turning to grayish brown near the origin that corresponds in color and R_F value to that in the chromatogram of *Standard solution 1*; one red-violet zone turning to grayish brown at an R_F about 0.08, corresponding in color and R_F value to that in the chromatogram of the *Standard solution 2;* above these spots a grayish brown zone may be present, corresponding in color and R_F value to that in the chromatogram of the *Standard solution 1;* and other colored zones of varying intensities may be observed in the chromatogram of the *Test solution.*

Total ash ⟨561⟩: not more than 10.0%.

Loss on drying ⟨731⟩—Dry it at 60° for 15 hours: it loses not more than 10.0% of its weight.

Foreign organic matter ⟨561⟩: not more than 5.0%.

Pesticide residues ⟨561⟩: meets the requirements.

Heavy metals ⟨231⟩: not more than 20 µg per g.

Extractable matter—Extract 2.00 g of the powdered material in a soxhlet apparatus with 150 mL of alcohol for 6 hours. Evaporate the solution to dryness under vacuum, and dry the residue at 105° for 24 hours.

⟨11⟩ USP Reference Standards

Add the following:

USP Pygeum Extract RS.

BRIEFING

Pygeum Extract; Pygeum Capsules. The chromatographic procedure for the *Content of sterols* is based on determinations performed with a capillary column HP-5 brand of G27 silica bonded stationary phase. Typical retention times are 12.5 minutes for 5α-cholestanol, 17.8 minutes for campesterol, 18.7 minutes for stigmasterol, and 19.0 minutes for β-sitosterol. The chromatographic procedure for the *Content of docosyl ferulate* is based on determinations performed on a Supersphere 60, RP-8 brand column of packing L7. The typical retention time for docosyl ferulate is about 12.5 minutes. See also the briefing under *Pygeum*.

(DSB: G. Giancaspro) RTS—37249-2

Add the following:

Pygeum Extract

» Pygeum Extract is prepared from the pulverized Pygeum using suitable solvents. It contains not less than 90 percent and not more than 110 percent of the labeled amount of docosyl ferulate and not less than 90 percent and not more than 110 percent of the labeled amount of total sterols as β-sitosterol.

Packaging and storage—Store in tight containers, protected from light.

Labeling—The label states the Latin binomial and, following the official name, the part of the plant from which the article was prepared. Label the content in percentage of total sterols as β-sitosterol and the content in percentage of docosyl ferulate. It also meets the requirements for labeling in the chapter *Extracts* ⟨565⟩.

USP Reference standards ⟨11⟩—*USP Pygeum Extract RS*. *USP* β-*Sitosterol RS*. *USP Docosyl Ferulate RS*.

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Test solution—Dissolve about 150 mg of Extract in 10 mL of chloroform. Apply 10 µL to the plate.

Standard solution 1—Prepare a solution of USP Pygeum Extract RS in chloroform having a concentration of about 15 mg per mL.

Standard solution 2—Prepare a solution of USP β-Sitosterol RS in chloroform having a concentration of about 2 mg per mL.

Developing solvent system: methylene chloride in a saturated chamber.

Spray reagent—Prepare a solution of sulfuric acid and water (1:1).

Procedure—Develop the chromatogram to a length of not less than 15 cm, and dry the plate in a current of air. Spray the plate with *Spray reagent*, and heat the plate at 100° for 10 minutes. Examine the plate under white light: the chromatogram obtained with the *Test solution* shows one red-violet zone turning to grayish brown near the origin that corresponds in color and R_F value to that in the chromatogram of *Standard solution 1*; one red-violet zone turning to grayish brown at an R_F of about 0.08 corresponding in color and R_F value to that in the chromatogram of *Standard solution 2*; above these spots a grayish brown zone may be present, corresponding in color and R_F value to that in the chromatogram of *Standard solution 1*; and other colored zones of varying intensities may be observed in the chromatogram of the *Test solution*.

B: The chromatogram of the *Test solution,* obtained as directed in the *Content of docosyl ferulate* exhibits peak for docosyl ferulate, the retention time of which corresponds to that exhibited by the *Standard solution*.

Loss on drying ⟨731⟩—Dry about 1.0 g of Extract, accurately weighed, for 3 hours at 110°: it loses not more than 10% of its weight.

Ash content ⟨561⟩: not more than 0.5%.

Heavy metals ⟨565⟩: meets the requirement.

Residual solvents ⟨565⟩: meets the requirement.

Pesticide residue ⟨561⟩: meets the requirement.

Aflatoxins ⟨561⟩: not more than 4 µg per kg of total aflatoxins B1, B2, G1, and G2; not more than 2 µg per kg of aflatoxin B1.

Microbial limits ⟨2021⟩—The total aerobic microbial count does not exceed 10^4 per g, the total combined molds and yeasts count does not exceed 10^3 per g, and it meets the requirements of the tests for absence of *Salmonella* species, and *Escherichia coli*.

Content of sterols—

Derivatizing solution: a mixture of bis(trimethylsilyl)acetamide and trimethylchlorosilane (9:1).

Internal standard solution—Prepare a solution containing 2 mg per mL of 5α-cholestane in chloroform.

System suitability solution—Prepare a solution containing about 2 mg per mL each of campesterol, stigmasterol, and USP β-Sistosterol RS. Transfer 2.0 mL of this solution and 2.0 mL of *Internal standard solution* to a 10-mL volumetric flask, and dilute with chloroform to volume. Evaporate about 500 µL of this solution to dryness using a stream of nitrogen. Dissolve the residue in 80 µL of *Derivatizing solution* and 20 µL of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Standard stock solution—Prepare a solution of USP β-Sitosterol RS in chloroform having a known concentration of about 2.0 mg per mL.

Standard solution—Transfer 2.0 mL of the *Standard stock solution* and 2.0 mL of *Internal standard solution* to a 10-mL volumetric flask, and dilute with chloroform to volume. Evaporate about 500 µL of this solution to dryness using a stream of nitrogen. Dissolve the residue in 80 µL of *Derivatizing solution* and 20 µL of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Test solution—Transfer an accurately weighed quantity of about 100 mg of Extract into a 100-mL, round-bottomed flask. Add 2.0 mL of *Internal standard solution* and 20 mL of diluted hydrochloric acid. Attach a condenser, and reflux in a bath at 100° for 30 minutes. Cool the solution to room temperature, and adjust by the addition of about 5 mL of 10 N sodium hydroxide to a pH of 8. Extract twice using 50 mL of ether each time, wash the collected organic phases with 50 mL of water, and evaporate the organic phase to dryness under vacuum. Dissolve the residue with 4 mL of chloroform, and transfer to a cartridge containing 500 mg of packing L8 that has been conditioned with a 2-column volume of *n*-hexane [Note—A suitable cartridge is Chromabond NH2, manufactured by Macheray Nagel, or equivalent.] Collect the eluate. Elute twice with a 1-column volume of a mixture of chloroform and isopropanol (2:1). Combine the eluates, and evaporate to dryness. Dissolve the residue in 10 mL of chloroform. Evaporate about 500 µL of this solution to dryness under a stream of nitrogen. Dissolve the residue with 80 µL of *Derivatizing solution* and 20 µL of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a split injection system, a flame-ionization detector, and a 0.32-mm × 30-m capillary column coated with a G27 phase of 0.25-µm thickness. The chromatograph is programmed as follows. Initially the temperature of the column is equilibrated at 250° for 5 minutes, then the temperature is increased at a rate of 5° per minute to 320°. The injection port and detector temperature are both maintained at 285°. The carrier gas is helium, with a flow rate adjusted to obtain a retention time of about 19 minutes for β-sitosterol, a split ratio of 1:50, and the make up is helium. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.66, 0.94, 0.96, and 1.00 for 5α-cholestane, campesterol, stigmasterol, and β-sitosterol, respectively; the resolution, *R*, between campesterol and stigmasterol is not less than 2;

the column efficiency is not less than 150,000 for the 5α-cholestane peak; and the tailing factor for each relevant peak is not more than 2.0.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Identify the signals corresponding to the relevant analytes by comparison with the chromatograms obtained with the *System suitability solution*.

Separately calculate the percentages of campesterol, stigmasterol, and β-sitosterol respectively in the portion of Extract taken by the formula:

$$200C/W(R_U/R_S),$$

in which C is the concentration of β-sitosterol, in mg per mL, in the *Standard solution; W* is the weight, in mg, of the Extract taken to prepare the *Test solution;* R_U is the ratio of the appropriate sterol peak to the internal standard in the chromatogram of the *Test solution;* and R_S is the ratio of the β-sitosterol peak to the 5α-cholestane internal standard in the chromatogram of the *Standard solution*. Calculate the total content of sterols in percentage by adding the individual percentages.

Content of docosyl ferulate—

Solution A—Use mixture of methanol and water (95:5).

Solution B—Use a filtered and degassed mixture of *Solution A* and acetonitrile.

Mobile phase—Use variable mixtures of *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Docosyl Ferulate RS with chloroform and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.02 mg per mL. Filter with a 0.45-µm membrane or finer porosity.

Test solution—Weigh approximately 250 mg of Extract. Add 5 mL of chloroform, and quantitatively transfer to a 25-mL volumetric flask. Dilute with acetonitrile to volume, and mix. Filter with a 0.45-µm membrane or finer porosity discarding the first 4 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 323-nm detector and a 4-mm × 25-cm column that contains packing L7, and is maintained at a temperature of 25°. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the column efficiency for the peak of docosyl ferulate is not less than 1700 theoretical plates; and the tailing factor for docosyl ferulate is not more than 2.0.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution*, and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the analyte peaks. Calculate the percentage of docosyl ferulate in the portion of Extract taken by the formula:

$$2500C/W(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Docosyl Ferulate RS in the *Standard solution; W* is the weight, in mg, of the portion of Extract taken to prepare the *Test solution;* and r_U and r_S are the peak responses for docosyl

ferulate in the *Test solution* and the *Standard solution*, respectively.

⟨11⟩ **USP Reference Standards**

Add the following:

USP Docosyl Ferulate RS.

BRIEFING

Pygeum Capsules—See briefings under *Pygeum* and *Pygeum Extract*.

(DSB: G. Giancaspro) RTS—37249-3

Add the following:

Pygeum Capsules

» Pygeum Capsules contain Pygeum Extract. Capsules contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of Extract, calculated as sterols and docosyl ferulate.

Packaging and storage—Preserve in tight containers at controlled room temperature.

Labeling—The label states the Latin binomial and, following the official name, the article from which the Capsules were prepared. The label also indicates the amount of Extract, in mg per Capsule. Label the Capsules to indicate the amount of sterols and docosyl ferulate in percentage of the Extract contained in the Capsules.

USP Reference standards ⟨11⟩—*USP* β-*Sitosterol RS. USP Pygeum Extract RS. USP Docosyl Ferulate RS.*

Identification—

A: The chromatogram of the *Test solution*, obtained as directed in the *Content of sterols*, exhibits peaks for campesterol, stigmasterol and β-sitosterol, the retention times of which correspond to those exhibited by the *Standard solution*.

B: The chromatogram of the *Test solution*, obtained as directed in the *Content of docosyl ferulate*, exhibits a peak for docosyl ferulate, the retention time of which corresponds to that exhibited by the *Standard solution*.

Disintegration ⟨2040⟩: meet the requirements for disintegration of botanical dosage forms.

RUPTURE TEST—[NOTE—See *Dissolution* ⟨711⟩ for *Apparatus*.]

Medium: simulated gastric fluid TS; 500 mL.

Apparatus 2: 50 rpm.

Time: 15 minutes.

Procedure—Place 1 Capsule in each vessel, and allow the Capsule to sink to the bottom of the vessel before starting rotation of the blade. Observe the Capsules, and record the time taken for each capsule shell to rupture.

Tolerances—The requirements are met if all of the Capsules tested rupture in not more than 15 minutes. If 1 or 2 of the Capsules rupture in more than 15 but not more than 30 minutes, repeat the test on 12 additional Capsules. Not more than 2 of the total of 18 Capsules tested rupture in more than 15 but not more than 30 minutes.

Weight variation ⟨2091⟩: meet the requirements.

Microbial limits ⟨2021⟩—The total bacterial count does not exceed 10^3 per g. The total combined molds and yeasts count does not exceed 10^2 per g. It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

Content of sterols—

Derivatizing solution, *Internal standard solution*, *System suitability solution*, *Standard stock solution*, *Standard solution*, and *Chromatographic system*—Proceed as directed in *Pygeum Extract*.

Test solution—Transfer an accurately weighed quantity of Capsules, equivalent to about 100 mg of the labeled amount of Extract, into a 100-mL, round-bottomed flask. Add 2.0 mL of *Internal standard solution* and 20 mL of diluted hydrochloric acid. Attach a condenser, and reflux in a bath at 100° for 30 minutes. Cool the solution to room temperature, and adjust by the addition of about 5 mL of 10 N sodium hydroxide to a pH of 8. Extract twice using 50 mL of ether each time, wash the collected organic phases with 50 mL of water, and evaporate the organic phase to dryness under vacuum. Dissolve the residue with 4 mL of chloroform, and transfer to a cartridge containing 500 mg of packing L8 that has been conditioned with a 2-column volume of *n*-hexane. [NOTE—A suitable cartridge is Chromabond NH2, manufactured by Macheray Nagel, or equivalent.] Collect the eluate. Elute twice with a 1-column volume of a mixture of chloroform and isopropanol (2:1). Combine the eluates, and evaporate to dryness. Dissolve the residue in 10 mL of chloroform. Evaporate about 500 µL of this solution to dryness under a stream of nitrogen. Dissolve the residue with 80 µL of *Derivatizing solution* and 20 µL of pyridine. Allow to stand for not less than 10 minutes at room temperature.

Procedure—Proceed as directed in *Pygeum Extract*. Separately calculate the content, in mg, of campesterol, stigmasterol, and β-sitosterol, respectively in the portion of Capsules taken by the formula:

$$2C(R_U / R_S),$$

in which C is the concentration of β-sitosterol, in mg per mL, in the *Standard solution;* R_U is the ratio of the appropriate sterol peak to the internal standard in the chromatogram of the *Test solution;* and R_S is the ratio of the β-sitosterol peak to the 5α-cholestane internal standard in the chromatogram of the *Standard solution*. Calculate the total content of sterols, in mg, by adding the individual contents.

Content of docosyl ferulate—

Solution A, *Solution B*, *Mobile phase*, and *Chromatographic system*—Proceed as directed for the *Content of docosyl ferulate* in *Pygeum Extract*.

Standard solution—Dissolve an accurately weighed quantity of USP Docosyl Ferulate RS with chloroform, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.01 mg per mL. Filter with a 0.45-µm membrane or finer porosity.

Test solution—Accurately weigh the contents of not fewer than 20 Capsules, and transfer an accurately weighed quantity of the material, equivalent to 0.2 mg of the labeled amount of docosyl ferulate, to a 50-mL beaker. Add 5 mL of chloroform, and dissolve in an ultrasonic bath. Transfer to a 20-mL volumetric flask with the aid of not more than 2 mL of chloroform. Dilute with acetonitrile to volume, and mix. Filter through a 0.45-µm membrane or finer porosity.

Procedure—Proceed as directed for the *Procedure* under *Content of docosyl ferulate* in *Pygeum Extract*, except to inject about 30 µL into the chromatograph. Calculate the content of docosyl ferulate, in mg, in the portion of Capsules taken by the formula:

$$20C(r_U / r_S),$$

in which the terms are as defined therein.

Container Specifications for Capsules and Tablets

Add the following:

Pygeum Capsules	T

STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

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Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in the *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

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Abstract—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

References—Consult a current copy of the *Pharmacopeial Forum* and the *ACS Style Guide* for assistance with reference style.

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An Atomic Spectroscopic Method as an Alternative to Both USP *Heavy Metals* ⟨231⟩ *and USP Residue on Ignition* ⟨281⟩

Tiebang Wang,[1] Jane Wu, Xiujuan Jia, Xiaodong Bu, Ivan Santos, and Richard S. Egan, *Analytical Research Department, Merck Research Laboratories, Merck & Co., Inc.*

ABSTRACT A multi-element inductively coupled plasma–mass spectrometry (ICP–MS) method has been demonstrated to be a suitable alternative to both USP *Heavy Metals* ⟨231⟩ and USP *Residue on Ignition* ⟨281⟩ for drug substances, intermediates, and raw materials. This ICP–MS method, combined with a direct-dissolution sample preparation procedure, is simpler, faster, more sensitive, and element specific. It consumes less sample and provides semiquantitative to quantitative results covering all elements of pharmaceutical interest and offers other advantages discussed herein.

INTRODUCTION

Metal or inorganic contamination of bulk drug substances, intermediates, and raw materials may be introduced in many ways, e.g., from reagents, solvents, electrodes, reaction vessels, plumbing and other equipment used in the synthesis, as well as via exposure to airborne particles or from container–closure systems. Most importantly, metals may be introduced by the utilization of catalysts at various steps during the synthesis. Because metals can catalyze decomposition and are potentially toxic, the metal content of process intermediates and final drug substances is widely monitored.

The United States Pharmacopoeia (USP) *Heavy Metals* ⟨231⟩ and similar tests provided in the European Pharmacopoeia (Ph. Eur.) and the Japanese Pharmacopoeia (JP) (*1–3*), consist of the precipitation of metal sulfides from an aqueous solution and the visual comparison of the color of that preparation to the color of a simultaneously and similarly treated standard lead solution. In order to obtain an aqueous solution for testing, ignition and combustion of the samples in a muffle furnace is often required in a preliminary step. In addition, after one adjusts the pH and adds either freshly prepared hydrogen sulfide or thioacetamide–glycerin base TS, the colors of the different metal sulfides range from white to yellow, orange, brown, and black (*4*), making the visual comparison with the dark brown–colored lead sulfide difficult. Furthermore, apart from the colors of the formed sulfides, there is no information about the identities of the metals that caused the positive result.

USP *Residue on Ignition (ROI)* ⟨281⟩ (*5*) and the similar sulfated ash limit test in Ph. Eur. also do not provide any information about the identity of inorganic impurities in the samples. These tests consist of heating 1 to 2 g of the sample in a suitable crucible that previously has been ignited, cooled, and weighed until the substance is thoroughly charred. The charred substance is then moistened by 1 mL of sulfuric acid, heated again until white fumes no longer are evolved, and ignited at 800 ±25° until the carbon is consumed. The residue is then cooled in a desiccator before it is weighed to determine the percentage of residue. Sometimes this procedure must be repeated in order to get a constant weight of the residue.

For USP *Heavy Metals* ⟨231⟩, Pb, Hg, Bi, As, Sb, Sn, Cd, Ag, Cu, and Mo typically will respond, but for USP *Residue on Ignition* ⟨281⟩, all elements that potentially react with sulfuric acid to form sulfated ash will respond. However, we observe that most of the time the alkaline and alkaline earth elements produce substantial amounts of sulfated ash.

Although both methods are still widely accepted and used in the pharmaceutical industry, they are nonspecific, insensitive, time-consuming, and labor intensive. USP *Heavy Metals* ⟨231⟩ has been shown to be suitable only for a few limited elements and has not been shown to be equally sensitive to all. In our laboratory it frequently yields either low recoveries or erroneous results. USP *ROI* ⟨281⟩ is not applicable to drug substances that are inorganic (e.g., sodium) salts. In addition, each test consumes a minimum of 1 to 2 g of sample, which can be a major problem when the quantities of the intermediates or the drug substances to be tested are limited.

Attempts have been made to improve these pharmacopeial methods to alleviate some of the limitations and shortcomings, but no major improvements have been achieved (*6–7*). We have recently published an ICP–MS method as an alternative to USP *Heavy Metals* ⟨231⟩ (*8*) and now wish to provide justification to expand its use to also cover USP *ROI* ⟨281⟩.

NEW TECHNOLOGY

Since 1980 ICP–MS has emerged as a major and powerful technique in elemental analysis (*9*), an area traditionally dominated by optical atomic spectrometry methods. In approximately 10 years, ICP–MS has progressed from a laboratory experiment to commercial development and wide-

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spread analytical application (*10–16*). This growth is fueled primarily by the fact that ICP–MS offers extremely low detection limits that range from sub–part per billion (ppb) to sub–part per trillion (ppt) detection limits for most elements. In most cases, these detection limits are 100 to 1000 times superior to those that can be routinely achieved by Inductively Coupled Plasma–Atomic Emission Spectrometry (ICP–AES). In addition, these detection limits are broadly achieved for almost all elements across the periodic table. Furthermore, the simpler mass spectra versus the much more complex optical spectra of the elements make this technique a quick tool for automated qualitative, semiquantitative, and quantitative elemental analysis.

In view of the superior and broad detection capability of ICP–MS and also because of the limitations inherent in USP *Heavy Metals* ⟨231⟩ and USP *Residue on Ignition* ⟨281⟩ prescribed by USP and Ph. Eur., a multi-element survey type ICP–MS method has been developed and employed at Merck as an alternative method. This method analyzes all sulfide-forming and sulfate-forming elements plus other elements with greatly enhanced specificity, sensitivity, speed, precision, and accuracy. In addition, because only part-per-million (ppm) levels of metals of pharmaceutical interest will be noted and reported, data processing and interpretation are also extremely simple. In most cases, a 5-second glance at the raw data will reveal the answers to the corresponding equivalent USP limit tests—that is, they pass or fail the limit tests for both heavy metals and *ROI* in a single run because more than 95% of the compounds tested contain no significant amount of inorganic impurities.

SAMPLE PREPARATION

In addition to the extreme sensitivity and specificity of the ICP–MS method, the sample preparation scheme for the simultaneous *Heavy Metals* and *ROI* tests is also simple and straightforward. Experience of handling thousands of pharmaceutical samples reveals that at least 99% of these samples are readily soluble in 80% (v/v) nitric acid solution. On some occasions, sonication may be needed to solubilize the samples or speed up their solubilization. In rare cases when samples do not dissolve, either a microwave digestion method can be used or the USP *Heavy Metals* and *ROI* tests can be carried out as usual. With the method proposed in this article, each sample can be prepared and analyzed in less than 15 minutes after initialization of the instrument, provided no microwave digestion is needed. By contrast, the USP *Heavy Metals* and *ROI* tests may each take several hours or longer to perform for one sample, particularly when sample combustion/digestion is involved. Another advantage of the proposed method is that only about 10 to 100 mg of sample is consumed for both the *Heavy Metals* and *ROI* tests using the ICP–MS method.

Furthermore, for potent compounds and other hazardous materials, the samples are denatured in 80% (v/v) nitric acid during the sample preparation procedure, and the dissolved samples can be analyzed safely using the ICP–MS method. In contrast, to perform the USP *Heavy Metals* test and particularly the USP *ROI* test, expensive and cumbersome containment facilities are required during sample preparation. In most laboratories, this would render the USP *Heavy Metals* and *ROI* tests impractical for potent and hazardous compounds.

METHOD PROCEDURE

Instrumentation—A Perkin-Elmer Elan 6000 Inductively Coupled Plasma–Mass Spectrometer (ICP–MS) equipped with an AS-91 auto-sampler was used throughout this study. The instrumental conditions and general method parameters are listed in *Table 1*.

Sample Analysis—After instrument warm-up (30–40 minutes), a two-point calibration of the ICP–MS is carried out by analyzing the calibration blank (80% nitric acid solution) and the mixed 69-element calibration standard (20 µg/L for all elements except Na, Si, P, K, Ca, and Fe, which are 1000 µg/L). All regulatory samples are spiked at a level equivalent to 10 mg/kg (10 ppm) of the metals that are sensitive to USP *Heavy Metals* ⟨231⟩ in solid sample (10 µg/L in solution). A spike recovery of 60–140% is required for each element. To monitor the drift of the instrument, the mixed 69-element standard (ICP–MS) is reanalyzed as a sample every 10 samples and at the end of the analysis.

REPORTING RESULTS

A) Heavy Metals Test—If those elements sensitive to the USP Heavy Metals test or the sum of these elements are found to have a concentration of higher than 10 ppm, the sample should be reanalyzed for those specific elements by a different atomic spectroscopic method such as ICP–AES and/or atomic absorption spectrometry.

B) ROI Test—Results from the ICP–MS analysis will be used for the conversions from ppm cations to the equivalent USP *ROI* ⟨281⟩ unless a % *ROI* result of higher than 0.05% is obtained. In this case, those elements with concentrations higher than their corresponding Limits of Quantitation or 10 ppm (whichever is larger) should be analyzed by a different atomic spectroscopic method (such as ICP–AES and/or atomic absorption spectrometry), and the results from the ICP–AES and/or atomic absorption spectrometry will be used for the conversions from ppm cations to the equivalent USP ⟨281⟩ *ROI.*

METHOD VALIDATION

Validation of the method for use as an alternative to the USP *Heavy Metals* ⟨231⟩ test was provided in our recent publication (8). That validation is also applicable for use of the method as an alternative for USP *ROI* ⟨281⟩, and the data will not be repeated here.

In summary, the analysis of National Institute of Standards and Technology (NIST) 1643d (Trace Elements in Water) standard reference material and the spiking experiments showed excellent to acceptable accuracy for a semi-quantitative method, with the exception of Fe (results shown in *Table 2*). The erroneously high data for Fe using both ^{54}Fe and ^{57}Fe result from spectral interferences mainly from $^{14}N^{40}Ar$, $^{16}O^{38}Ar$, and $^{40}Ar^{16}O^{1}H$, which cannot be circumvented with the current instrument capabilities. Spiked samples also demonstrated acceptable method precision, and spiked blanks provided Limit of Detection (LOD) and Limit of Quantitation (LOQ) values that were below part-per-million (ppm) levels for all elements of pharmaceutical interest. The LOD and LOQ values are provided in *Table 3*.

Matrix effects and spectral interference—Positive results at moderate levels for some elements in the presence of one or more other high-level elements should always be investigated further for spectral interferences or by confirming the results with an alternative method such as ICP–AES or Graphite Furnace Atomic Absorption Spectroscopy (GFAAS). Matrix effects are minimized by running the calibration blank and calibration standard in the same matrix as in the samples and by dissolving a minimum amount of sample in the solution to be analyzed (0.1% total dissolved solids), taking advantage of the extremely high sensitivity of the ICP–MS. Spectral interferences are monitored by using more than one isotope for the same element whenever possible for some interference-prone low-mass elements.

EQUIVALENCE OF THE ICP–MS METHOD TO USP ⟨281⟩ *ROI*

A demonstration of the equivalence of the ICP–MS method and the USP ⟨281⟩ *ROI* procedure was provided by the analysis of six typical drug substances by both methods. The results are given in *Table 4* and *Table 5*. The agreements are excellent.

UTILIZATION OF THE METHOD

A survey method that permits simultaneous qualitative to quantitative detection (depending on the elements and the concentration levels) of up to 69 elements, including all those of pharmaceutical interest, in less than 15 minutes would be viewed by some as a giant leap forward compared to traditional USP methods. The use of such a method, which employs a very sophisticated and expensive instrument, as an alternative to a seemingly economical wet chemical test that has been in use for decades would be viewed by others as technological overkill.

We take a less extreme view and believe that because the equipment is already present in the laboratory to address other very challenging analytical problems, its application to more mundane uses is simply good resource management. We have found that the extensive use of the ICP–MS for this elemental survey analysis does not degrade its capability for even more challenging tasks.

CONCLUSION

The proposed method uses direct dissolution of the samples in 80% nitric acid solution combined with ICP–MS as the analytical tool. It is an attractive alternative method for both USP *Heavy Metals* ⟨231⟩ and USP *ROI* ⟨281⟩. The availability of the ICP–MS in the laboratory offers much more rapid, sensitive, precise, simple, and element-specific analysis. Furthermore, it consumes far less sample and is safely applicable to potent compounds and other hazardous materials.

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Table 1. Elan 6000 Instrumental Conditions and Method Parameters

RF power	1300 W
Coolant argon flow	15.0 L/min
Auxiliary argon flow	1 L/min
Nebulizer argon flow	0.86–1.06 L/min
Sample introduction system	Cross-flow nebulizer with Scott spray chamber
Operating frequency	40 MHz
Sample uptake rate	1.5 mL/min
Detector mode	Dual mode
Sampler/skimmer cones	Platinum
Scanning mode	Peak hopping
Number of points/peak	1
Dwell time	15 ms
Sweeps/reading	40
Number of replicates	2

Table 2. Calibration Verification with NIST 1643d in 80% HNO_3 Matrix

Element	Isotope	Measured Concentration (ppm)	Certified or Reference (*) Value by NIST (ppm)
Li	7	0.0168	0.01815 ±0.00064
Be	9	0.0115	0.01253 ±0.00028
B	11	0.127	0.1448 ±0.0052
Na	23	21.9	22.07 ±0.64
Mg	24	8.5	7.989 ±0.035
Al	27	0.115	0.1276 ±0.0035
Si	28	3.28	2.7*
P	31	<LOQ	No certified or reference value
K	39	2.37	2.356 ±0.035
Ca	44	33.7	31.04 ±0.64
Sc	45	<LOQ	No certified or reference value
Ti	48	<LOQ	No certified or reference value
Ti	49	<LOQ	No certified or reference value
V	51	0.0361	0.0351 ±0.0014
Cr	52	0.0185	0.01853 ±0.00020
Cr	53	0.0194	0.01853 ±0.00020
Mn	55	0.0389	0.03766 ±0.00083
Fe	54	0.9383	0.0912 ±0.0039
Fe	57	0.1596	0.0912 ±0.0039
Co	59	0.0255	0.02500 ±0.00059
Ni	58	0.0596	0.0581 ±0.0027
Ni	60	0.0612	0.0581 ±0.0027
Cu	63	0.0205	0.0205 ±0.0038
Cu	65	0.0217	0.0205 ±0.0038
Zn	64	0.085	0.07248 ±0.00065
Zn	66	0.0782	0.07248 ±0.00065
Ga	69	<LOQ	No certified or reference value
Ge	72	<LOQ	No certified or reference value

Table 2. Calibration Verification with NIST 1643d in 80% HNO_3 Matrix *(Continued)*

Element	Isotope	Measured Concentration (ppm)	Certified or Reference (*) Value by NIST (ppm)
As	75	0.053	0.05602 ±0.00073
Se	77	0.0107	0.01143 ±0.00017
Se	82	0.00944	0.01143 ±0.00017
Rb	85	0.0125	0.013*
Sr	88	0.349	0.2948 ±0.0034
Y	89	<LOQ	No certified or reference value
Zr	90	<LOQ	No certified or reference value
Nb	93	<LOQ	No certified or reference value
Mo	95	0.117	0.1129 ±0.0017
Ru	101	<LOQ	No certified or reference value
Rh	103	<LOQ	No certified or reference value
Pd	105	<LOQ	No certified or reference value
Ag	107	0.00135	0.001270 ±0.000057
Cd	111	0.00664	0.00647 ±0.00037
In	115	<LOQ	No certified or reference value
Sn	118	0.0038	No certified or reference value
Sn	120	0.00374	No certified or reference value
Sb	121	0.0524	0.0541 ±0.0011
Te	125	0.000991	0.001*
Cs	133	0.00432	No certified or reference value
Ba	137	0.507	0.5065 ±0.0089
La	139	<LOQ	No certified or reference value
Ce	140	<LOQ	No certified or reference value
Pr	141	<LOQ	No certified or reference value
Nd	146	<LOQ	No certified or reference value
Sm	147	<LOQ	No certified or reference value
Eu	153	<LOQ	No certified or reference value
Gd	157	<LOQ	No certified or reference value
Tb	159	<LOQ	No certified or reference value
Dy	163	<LOQ	No certified or reference value
Ho	165	<LOQ	No certified or reference value
Er	166	<LOQ	No certified or reference value
Tm	169	<LOQ	No certified or reference value
Yb	172	<LOQ	No certified or reference value
Lu	175	<LOQ	No certified or reference value
Hf	178	<LOQ	No certified or reference value
Ta	181	<LOQ	No certified or reference value
W	182	<LOQ	No certified or reference value
Re	185	<LOQ	No certified or reference value
Os	189	<LOQ	No certified or reference value
Ir	193	<LOQ	No certified or reference value
Pt	195	<LOQ	No certified or reference value
Au	197	<LOQ	No certified or reference value

Table 2. Calibration Verification with NIST 1643d in 80% HNO_3 Matrix *(Continued)*

Element	Isotope	Measured Concentration (ppm)	Certified or Reference (*) Value by NIST (ppm)
Hg	202	<LOQ	No certified or reference value
Tl	205	0.00791	0.00728 ±0.00025
Pb	208	0.019	0.01815 ±0.00064
Bi	209	0.014	0.013*
Th	232	<LOQ	No certified or reference value
U	238	<LOQ	No certified or reference value

Table 3. LODs and LOQs

Element	Isotope	80% HNO_3 Solution	
		LOD (ppm)	LOQ (ppm)
Li	7	0.1	0.5
Be	9	0.08	0.3
B	11	6	22
Na	23	0.3	1
Mg	24	0.2	0.6
Al	27	5	16
Si	28	35	115
P	31	230	766
K	39	1	4
Ca	44	4	12
Sc	45	1	4
Ti	48	0.3	1
Ti	49	0.07	0.2
V	51	0.02	0.08
Cr	52	0.06	0.2
Cr	53	0.08	0.3
Mn	55	0.03	0.09
Fe	54	148	493
Fe	57	1	4
Co	59	0.01	0.05
Ni	58	3	8
Ni	60	2	5
Cu	63	0.05	0.2
Cu	65	0.09	0.3
Zn	64	6	20
Ga	69	0.01	0.05
Ge	72	0.03	0.1
As	75	0.06	0.2
Se	77	0.5	2
Se	82	0.8	3
Rb	85	0.01	0.03

Table 3. LODs and LOQs *(Continued)*

Element	Isotope	80% HNO_3 Solution	
Sr	88	0.01	0.03
Y	89	0.02	0.05
Zr	90	0.01	0.03
Nb	93	0.02	0.07
Mo	95	0.02	0.08
Ru	101	0.01	0.04
Rh	103	0.01	0.03
Pd	105	0.02	0.08
Ag	107	0.02	0.05
Cd	111	0.04	0.1
In	115	0.01	0.04
Sn	118	0.02	0.05
Sb	121	0.02	0.08
Te	125	0.2	0.6
Cs	133	0.01	0.02
Ba	137	0.02	0.06
La	139	0.01	0.03
Ce	140	0.01	0.02
Pr	141	0.01	0.03
Nd	146	0.01	0.05
Sm	147	0.02	0.05
Eu	153	0.01	0.02
Gd	157	0.02	0.06
Tb	159	0.01	0.03
Dy	163	0.01	0.04
Ho	165	0.01	0.03
Er	166	0.03	0.09
Tm	169	0.01	0.03
Yb	172	0.01	0.04
Lu	175	0.01	0.04
Hf	178	0.01	0.04
Ta	181	0.02	0.07
W	182	0.07	0.2
Re	185	0.01	0.05
Os	189	0.2	0.7
Ir	193	0.01	0.05
Pt	195	0.02	0.07
Au	197	0.04	0.1
Hg	202	0.05	0.2
Tl	205	0.01	0.03
Pb	208	0.01	0.04
Bi	209	0.01	0.04
Th	232	0.01	0.02
U	238	0.01	0.02

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Table 4. Comparison of USP ⟨281⟩ and ICP–MS *ROI* Results

Sample ID		Compound #1		Compound #2		Compound #3	
Elements	Sulfates Formed	ICP–MS Result (ppm)	Equivalent *ROI* (%)	ICP–MS Result (ppm)	Equivalent *ROI* (%)	ICP–MS Result (ppm)	Equivalent *ROI* (%)
Li	Li_2SO_4		0.000		0.000		0.000
Na	Na_2SO_4	463	0.138		0.000	262	0.081
Mg	$MgSO_4$		0.000		0.000		0.000
Al	$Al_2(SO_4)_3$		0.000		0.000		0.000
Si	SiO_2	22	0.005	24	0.005	17	0.004
K	K_2SO_4		0.000		0.000		0.000
Ca	$CaSO_4$	24	0.007		0.000	10	0.003
Ti	$Ti_2(SO_4)_3$		0.000		0.000		0.000
V	VSO_4		0.000		0.000		0.000
Cr	$Cr_2(SO_4)_3$		0.000		0.000		0.000
Mn	$MnSO_4$		0.000		0.000		0.000
Fe	$Fe_2(SO_4)_3$		0.000		0.000		0.000
Co	$CoSO_4$		0.000		0.000		0.000
Ni	$NiSO_4$		0.000		0.000		0.000
Cu	$CuSO_4$		0.000		0.000		0.000
Zn	$ZnSO_4$		0.000		0.000		0.000
Total *ROI* (%) by ICP–MS			**0.150**		**<0.05**		**0.088**
USP ⟨281⟩ *ROI* (%)			**0.12**		**<0.05**		**0.09**

Table 5. Comparison of USP ⟨281⟩ and ICP–MS *ROI* Results

Sample ID		Compound #4		Compound #5		Compound #6	
Elements	Sulfates Formed	ICP–MS Result (ppm)	Equivalent *ROI* (%)	ICP–MS Result (ppm)	Equivalent *ROI* (%)	ICP–MS Result (ppm)	ICP–MS Result (ppm)
Li	Li_2SO_4		0.000		0.000		0.000
Na	Na_2SO_4	10100	3.118		0.000		0.000
Mg	$MgSO_4$		0.000		0.000		0.000
Al	$Al_2(SO_4)_3$		0.000		0.000		0.000
Si	SiO_2	66	0.014		0.000		0.004
K	K_2SO_4		0.000		0.000		0.000
Ca	$CaSO_4$		0.00		0.000		0.000
Ti	$Ti_2(SO_4)_3$		0.000		0.000		0.000
V	VSO_4		0.000		0.000		0.000
Cr	$Cr_2(SO_4)_3$		0.000		0.000		0.000
Mn	$MnSO_4$		0.000		0.000		0.000
Fe	$Fe_2(SO_4)_3$		0.000		0.000		0.000
Co	$CoSO_4$		0.000		0.000		0.000
Ni	$NiSO_4$		0.000		0.000		0.000
Cu	$CuSO_4$		0.000		0.000		0.000
Zn	$ZnSO_4$		0.000		0.000		0.000
Total *ROI* (%) by ICP–MS			**3.132**		**<0.05**		**<0.05**
USP⟨281⟩ *ROI* (%)			**3.2**		**<0.05**		**<0.05**

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Biopharmaceutical Characterization of Herbal Medicinal Products

The FIP Working Group on Herbal Medicinal Products consists of the following experts: Dr. Friedrich Lang (Firma Schwabe, Karlsruhe, Germany, chair of the group),* Prof.-Dr. Konstantin Keller (Bundesinstitut für Arzneimittel und Medizinprodukte, Bonn, Germany), Dr. Michael Ihrig (Zentrallaboratorium Deutscher Apotheker, Eschborn, Germany), Joy van Oudtshoorn-Eckard (J & B Pharmaceutical Consultants, Pretoria, South Africa), Prof.-Dr. Helga Möller (Zentrallaboratorium Deutscher Apotheker, Eschborn, Germany), Dr. Srini Srinivasan (United States Pharmacopoeia, Rockville, MD), Dr. Yu He-ci (Hankintatukku OY, Finland)

ABSTRACT In this article, a working group of the International Pharmaceutical Federation (FIP) presents their revised discussion paper on the biopharmaceutical characterization of herbal medicinal products. This revision takes into account scientific contributions made after the first publication of the draft and has been substantially extended. Based on knowledge of their composition and efficacy, plant extracts can be classified into 3 categories: A, B, and C. In the case of substitution of herbal medicinal products containing extracts from category A, the Note for Guidance on the Investigation of Bioavailability and Bioequivalence (BA/BE) should fully be addressed. A waiver of bioequivalence studies or clinical studies is possible if justified according to the Note for Guidance (high solubility and rapid or similar dissolution). In the case of herbal medicinal products (HMPs) containing class B or C extracts, the Note for Guidance on BA/BE in principle should be considered. An assessment should be made concerning pharmaceutical equivalence of the extracts used in the test and reference formulations, their solubility under physiological conditions (>90%), and the dissolution profile of active and/or lipophilic markers. If no markers are available in the case of class C extracts, the dissolution test may be dropped if no problems are expected from the solubility characteristics of the extracts. A waiver of bioequivalence studies or clinical studies is possible if justified according to the Note for Guidance (high solubility and rapid or similar dissolution in comparison to the reference product). The therapeutic equivalence of HMPs containing class B and C extracts in many instances may be demonstrated by clinical studies rather than via BA/BE studies.

INTRODUCTION

In 1999 the FIP Special Interest Group (SIG) on the Quality of Pharmaceuticals established a working group to elaborate recommendations for biopharmaceutical characterization of Herbal Medicinal Products (HMPs). Considering the current European and American regulatory guidelines on quality for HMPs, the SIG embarked on a clarification of biopharmaceutical characteristics taking into account the new classification of HMPs. A first draft was published in *Die Pharmazeutische Industrie* [63(10), 2001] and *Pharmacopeial Forum* [28(1) 2002].

Comments meanwhile were collected by the authors and were integrated into the final version as far as possible. A scientific symposium dedicated to the topic was organized in Berlin by the German Pharmaceutical Society. Due to the complexity of the matter, not all scientific views could be harmonized. The publication is now updated and substantially extended. The issues of the pharmaceutical equivalence of plant extracts and dissolution from pharmaceutical formulations are clarified and integrated into the concept paper. Further aspects of the solubility of plant extracts have been elaborated. The decision trees are simplified and put into more concrete terms. The citation index has been extended. The FIP working group would like to emphasize that the present proposals form a discussion paper and are not binding recommendations. The group is aware that HMPs are not in all cases and countries regarded as part of the science-based medicine. Often plant extracts are used in the form of dietary supplements and food products. This publication deals mainly with scientifically accepted HMPs.

In contrast to chemically defined drug products, the biopharmaceutical quality and behavior of HMPs often are not well documented. In most cases an in vitro/in vivo biopharmaceutical characterization is complicated by the complex composition of herbal drug preparations, the extensive metabolism of constituents, and the resulting analytical difficulties. Further, the pharmacokinetics and bioavailability of HMPs are seldom described in the literature (*1*, *2*). The active pharmaceutical ingredient (API) of HMPs is generally defined to be the whole herbal preparation (the extract) in its entirety. Individual (or groups of) constituents have only in selected cases been identified as being responsible for the therapeutic activity of HMPs (see *Table 1*). HMPs containing raw plant material or teas, as well as liquid formulations, are not considered in this article. The existing tight network of rules concerning dissolution testing (*3*) and investigation of BA/BE (*4*) has not yet been transferred completely to HMPs. Early efforts in this direction include USP drafts of monographs on dietary supplement products that include dissolution testing (*5*) and a European Medical Evaluation Agency (EMEA) Note for Guidance on Specifications for HMPs (*6*).

In many cases it may be assumed (as is usual for chemically defined APIs also) that complete and rapid dissolution of the whole plant extract from a solid oral formulation is a prerequisite for nonproblematic bioavailability and clinical

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efficacy of HMPs. Some lipid extracts and essential oils, however, are not easily soluble and do not dissolve completely from the pharmaceutical formulation. Such extracts and formulations may be indicative of biopharmaceutical problems. Yet HMPs are often uncritically substituted by physicians, pharmacists, and patients. The present article proposes some scientific aspects and strategies concerning biopharmaceutical studies for HMPs from the same plant and suggests cases in which clinical or bioequivalence studies may be replaced or waived by in vitro studies.

SPECIAL ASPECTS AND CLASSIFICATION OF HMPs

Because the whole herbal drug preparation, i.e., the extract, is regarded as the active pharmaceutical ingredient, several extract classes, depending on the pharmaceutical-analytical, pharmacological-toxicological, and clinical findings, can be identified. [NOTE—this classification has been introduced in the general monograph "Extracta" of the *European Pharmacopoeia.*]

(A) *Standardized extracts* contain constituents (single or groups) that are solely responsible for the acknowledged and documented therapeutic activity. Standardization (adjustment) to a defined content is acceptable (e.g., standardized Senna leaf dry extract) using inert excipients or preparations with a higher or lower content.

(B) *Quantified extracts* contain chemically defined constituents (single or groups) possessing relevant pharmacological properties (active markers). These substances are likely to contribute to the clinical efficacy; however, evidence that they are solely responsible for such clinical efficacy is not yet available (e.g., extracts of Ginkgo or St. John's Wort). The characterization of these extracts should take into consideration as far as possible the particular state of knowledge concerning the documented efficacy, quality, and safety of an extract. Standardization by blending different lots of a herbal drug before extraction or by mixing different lots of herbal drug preparations is appropriate/acceptable. Adjustment/standardization using excipients is not acceptable.

(C) *Other extracts* contain no constituents documented as being determinant or relevant for efficacy or as having pharmacological or clinical relevance. In these cases, chemically defined constituents (markers) without known therapeutic activity may be used for control purposes (e.g., Valerian or Stinging Nettle Root Extract). These markers may be used to monitor Good Manufacturing Practices (GMPs) or as an indicator for the assay of the drug product.

This classification implies that an extract may be upgraded from class C to B and even to class A as further knowledge is acquired about the extract. The proposed classification seems to be useful to determine the scientific level and future efforts for a biopharmaceutical characterization of HMPs. *Table 1* lists some examples from the European and German Pharmacopoeias (*7*).

In many cases HMPs are based on traditionally known herbal materials and preparations (extracts). Their use is often well established but not based on systematic preclinical and clinical studies. HMPs may show great differences in the class of extracts used (even if they come from the same plant), the dosage forms, and strengths. In the case of substitution of one product for another, the importance of BA/BE has frequently been ignored in the past.

In only a few cases have HMPs been developed using documented pharmacological, toxicological, and clinical experimental studies involving traditional herbs (e.g., *Silibinum marianum* in Europe) or herbs originally not included for traditional use (e.g., *Ginkgo biloba*). These HMPs often contain concentrated or purified extracts in order to improve the dosage or to reduce side effects. For such new or highly developed HMPs, scientific aspects should be investigated if a product is intended to be substituted for the original approved herbal medicinal product.

THE IMPORTANCE OF THE NOTE FOR GUIDANCE ON THE INVESTIGATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

The current EMEA note for guidance on the investigation of BA/BE (designed in principle for chemically defined active substances) contains definitions and processes that may also be applicable to HMPs.

PHARMACEUTICAL EQUIVALENCE

Medicinal products are pharmaceutically equivalent if they contain the same amount of the same active substance(s) in the same dosage forms that meet the same or comparable standards. Pharmaceutical equivalence does not necessarily imply bioequivalence because differences in the excipients and/or the manufacturing process may lead to faster or slower dissolution and/or absorption.

PHARMACEUTICAL ALTERNATIVES

Medicinal products are pharmaceutical alternatives if they contain the same active moiety but differ in chemical form (salt, ester, etc.) of that moiety or in the dosage form or strength.

ESSENTIALLY SIMILAR PRODUCTS

A medicinal product is essentially similar to an original product when it satisfies the criteria of having the same qualitative and quantitative composition in terms of active substance(s), of having the same pharmaceutical form, and of being bioequivalent unless it is apparent in the light of scientific knowledge that it differs from the original product regarding safety and efficacy (see also "The Rules Governing Medicinal Products in the European Community," Notice to Applicants, Vol. 2A). By extension it is generally considered that for immediate-release products the concept of essential similarity also applies to different oral forms (tablets and capsules) with the same active substance. Concerns about differences in essentially similar medicinal products arise because of the use of different excipients and methods of manufacture that ultimately may have an influence on

safety and efficacy. In the case of immediate-release dosage forms, a bioequivalence study is the widely accepted means of demonstrating that these differences have no impact on the performance of the formulation with respect to rate and extent of absorption. It is desirable that excipients be devoid of any effect, that their safe use be ensured by appropriate warning in the package label, and that they not interfere with either the release or the absorption process. An essentially similar product can be used instead of the innovator product. The latter is a medicinal product authorized and marketed on the basis of a full dossier, i.e., one that includes chemical, biological, pharmaceutical, pharmacological-toxicological, and clinical data. A reference product thus must be an innovator product.

THERAPEUTIC EQUIVALENCE

A medicinal product is therapeutically equivalent to another product if it contains the same active substance or active moiety and clinically shows the same efficacy and safety as that product whose efficacy and safety has been established. In practice, demonstration of bioequivalence is generally the most appropriate method of substantiating therapeutic equivalence between medicinal products that are pharmaceutical equivalents or pharmaceutical alternatives, provided they contain only excipients that are generally recognized as not having an influence on safety and efficacy. However in some cases when similar extent of absorption but different rates of absorption are observed, the products still can be judged therapeutically equivalent if those differences are not of therapeutic relevance. A clinical study probably will be necessary to prove that differences in absorption rate are not therapeutically relevant.

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS)

The Biopharmaceutical Classification System was originally developed for chemically defined synthetic drug substances (*8*). BCS takes into account the physicochemical characteristics of a compound, in particular solubility (in aqueous buffer systems of physiological pH) and permeability (through gastrointestinal barriers simulated by in vitro and in vivo models). According to the BCS, APIs are classified into four groups (group I, high solubility–high permeability; group II, low solubility–high permeability; group III, high solubility–low permeability; group IV, low solubility–low permeability). In this context high solubility is defined so that the highest dosage strength is entirely soluble in 250 mL of buffer, and high permeability indicates that more than 80% of the dose is absorbed after oral administration. It seems to be scientifically plausible that the solubility and dissolution characteristics of an API may be much more pharmaceutically influenced and controlled than the permeability. According to BCS a waiver of BA/BE studies may be granted for Class I drugs. By extension a waiver has also been proposed for Class III drugs (*9*, *10*).

The solubility part of the BCS principles was recently integrated in the final Note for Guidance on the investigation of BA/BE concerning immediate-release dosage forms. The Note for Guidance confirms that the investigation of solubility and the rapid dissolution of an API are of greater importance than permeability. According to the Note for Guidance, in order to justify a waiver of in vivo bioequivalence studies in the case of products containing approved active substances, the following characteristics should be considered:

Characteristics related to the active substance:

- risk of therapeutic failure or adverse reactions
- risk of bioinequivalence
- pharmacokinetic properties.

Solubility: In general, when the active substance is highly water soluble the product could be exempted from bioequivalence studies unless, considering the other characteristics, the exemption could entail a potential risk. An active substance is considered highly water soluble if the amount contained in the highest dose strength of an immediate-release product can be dissolved in 250 ml of each of three buffers within the range of pH 1–8 at 37 °C (preferably at or about pH 1.0, 4.6, and 6.8).

Characteristics related to the medicinal product:

- excipients (no interaction expected)
- manufacture (not critical).

Rapid dissolution: To justify exemption from bioequivalence studies, in vitro data should demonstrate the similarity of dissolution profiles between the test product and the reference product in each of three buffers within the range of pH 1–8 at 37 °C (preferably at or about pH 1.0, 4.6, and 6.8). However in cases where more than 85% of the active substance is dissolved within 15 minutes, the similarity of the dissolution profiles may be accepted, and the f2 similarity values need not be calculated.

INTERPRETATION OF THE DEFINITIONS FOR HMPs

PHARMACEUTICAL EQUIVALENCE

Pharmaceutical Equivalence of Plant Extracts.

The definitions in the EMEA note for guidance on BA/BE were set with chemically defined active substances and finished products in mind. In contrast to synthetic drug substances, the composition of a plant extract is determined by the manufacturing process and the quality of the plant material. Only for plant extracts belonging to class A is it accepted that defined constituents are responsible for the therapeutic activity independent of the composition of other components. For example, milk thistle extracts containing between 40 and 80% of silymarin as known active constituents are regarded as pharmaceutically alternative even if not strictly pharmaceutically equivalent. This is similar to chemically defined APIs in the form of different salts that may be seen as pharmaceutical alternatives. In other words, in the case of class A extracts pharmaceutical equivalence is not relevant.

In the case of class B and C extracts the question of pharmaceutical equivalence is much more difficult. A strict interpretation of the above for HMPs would imply that extracts from the same plant are not pharmaceutically equivalent if manufactured by different methods and especially if one uses different extraction solvents. At present in order to check for pharmaceutical equivalence of class B and C extracts, at least the specified herbal material, the drug:extract ratio (DER), and the principal extraction method (mainly the primary extraction solvent) should be taken into account. Unfortunately these characteristics alone cannot guarantee constant composition of plant extracts and a clear evaluation of pharmaceutical equivalence.

Pharmaceutically equivalent extracts theoretically should be congruent concerning the qualitative and quantitative composition of all constituents. Pharmaceutical equivalence seems to be still more important if efficacy and safety have been exclusively demonstrated with an individual plant extract in a specific formulation and specification. From an analytical point of view full pharmaceutical equivalence is extremely difficult to demonstrate. Plant extracts may consist of hundreds or even thousands of constituents. Even if obtained from the same plant and using the same manufacturing procedure, extracts may be different. This may be caused by quality differences of the harvested plant material due to agricultural conditions and climate. For practical analytical reasons often only some chromatographic fingerprints may be examined. But even if fingerprints match (semi)quantitatively, actual differences in the chemical composition of two extracts cannot be excluded. In this context some have debated whether plant extracts obtained from the same plant using solvents with similar extraction power and similar extraction procedures could be seen (less strictly) as therapeutic alternatives. In many other cases the therapeutical indications will definitely be related to the product's manufacturing process, as in the example of *Ginkgo biloba* extract.

The question of pharmaceutical equivalence of extracts from the same plant thus has to be decided on two levels. First, for extracts described in medicinal monographs: If extracts from the same plant but different manufacturing methods are summarized in monographs of ESCOP, WHO, CORE-SPCs (EMEA), or others, they are acknowledged as therapeutically equivalent despite the differences of their composition. Second, for extracts not described in medicinal monographs, only extracts manufactured with the same process (e.g., solvent, DER) may be assumed to be pharmaceutically and therapeutically equivalent.

Pharmaceutical equivalence of the finished HMPs.

Different formulations using the same extracts (e.g., coated tablets or soft gelatin capsules, even immediate-release types) may not be regarded as pharmaceutical equivalents without evaluation of the dissolution characteristics of the extract; see "Comments and Examples" below.

SOLUBILITY

The BCS system as described above may be helpful for HMPs as well (*11*). For immediate-release HMPs the solubility of the whole extract and (if known) pharmacologically active constituents may be regarded as crucial characteristics for a waiver of bioequivalence or clinical studies. A specific feature of plant extracts (even if they are extracted with pure water) is, however, that the solubility characteristics may change after drying. After plant extracts are dissolved in aqueous systems, cloudy solutions may result because of polymeric residues caused by tannins, polyphenols, etc. On the other hand, turbidities and insoluble residues seen on rehydration may be caused by lipophilic constituents that are important for the therapeutic activity of the extract. It is, therefore, difficult to set an acceptance criterion for "highly soluble" in the case of a plant extract.

If it could be demonstrated that a nonsoluble residue of a plant extract consists only of nonspecific polymeric compounds such as polyphenols, phlobaphenes, proteides, etc. and does not contain low-molecular-weight constituents assumed to possess pharmacological activity, then a solubility of >90% would seem to be adequate for the characterization of an extract as highly soluble. Under that condition and if the other requirements of the Note for Guidance (see above) are fulfilled, a waiver of clinical or bioequivalence studies may be acceptable in the case of substitution of HMPs.

IN VITRO DISSOLUTION OF HMPs

In vitro dissolution testing is performed to determine the rate and quantity of active drug substances dissolved in a specific time. It is an important tool to characterize during the development phase the biopharmaceutical quality of finished drug formulations containing chemically defined drug substances and is used as a further control of marketed products. Comprehensive Guidelines for Dissolution Testing of Solid Oral Products have been established by FIP (*3*).

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The EMEA Note for Guidance on specifications of HMPs in principle includes dissolution tests that may, however, be omitted in the case of immediate-release HMPs that do not contain constituents with known therapeutic activity (the Note for Guidance assumes that all conventional solid oral dosage forms with rapid disintegration are immediate-release HMPs). The EMEA Note for Guidance on specifications does not distinguish between HMPs containing standardized, quantified, or other extracts. In accordance with the EMEA Note for Guidance on specifications, disintegration instead of dissolution testing may be sufficient for rapidly dissolving products containing herbal drug preparations that are highly soluble throughout the physiological pH range. Acceptance criteria with a single-point measurement are appropriate for immediate-release drug products. Multiple-point acceptance criteria are necessary for modified-release dosage forms only.

The EMEA concept should be extended along the following lines: Pharmaceutical formulations containing class A extracts should be characterized for the in vitro release of the active constituent(s) because dissolution characteristics different from those expected from the solubility cannot be excluded. For extracts of class B or C where the plant extract as a whole is the API, a holistic description of the in vitro dissolution behavior of all constituents usually is not feasible. Sometimes groups of constituents may be analyzed with fingerprint techniques such as HPLC with photodiode array detection. Only in selected cases will it be possible to use nonspecific methods (for example gravimetric analysis) and thus to characterize the dissolution of the whole extract (*12*). If pharmacologically active markers are known (class B) they may be used as dissolution markers. This makes sense especially if the chosen marker is not very soluble in aqueous systems and therefore may serve as a true indicator of potential dissolution problems. The same is valid for class C extracts if a reliable and representative dissolution marker can be found.

For example, Valerian extracts (class C) contain about 0.5% valerenic acid. Valerenic acid is rather lipophilic and seems to be suitable as a dissolution indicator. Ginkgo extracts contain lipophilic ginkgolides that may be traced analytically for dissolution testing (*13*, *14*). In the case of St. Johns Wort extract, hyperforin or hypericines are useful dissolution markers (*15*). Recently some dissolution indicators have been proposed in *USP–NF* monographs for multivitamin preparations (*16*).

Summarizing:

Class A The API is standardized to a defined content of the active constituent. The dissolution test is feasible. The dissolution profiles of the reference and test products may be compared and checked for rapid or similar dissolution.

Class B The API is quantified concerning defined constituents (active markers). These substances contribute to the clinical efficacy. The dissolution test is feasible for active markers. Other dissolution-indicating markers may be used if justified. The dissolution profiles of the reference and test products may be compared and checked for rapid or similar dissolution.

Class C No constituents are known to be relevant for pharmacological and therapeutical effects. Dissolution-indicating markers may be used in order to compare the dissolution profiles of the reference and test products and to check for rapid or similar dissolution. If it is not feasible (if no marker can be found or no holistic method is available), the dissolution test may be dropped if no problems may be expected from the solubility characteristics of the extract.

DECISION STRATEGIES

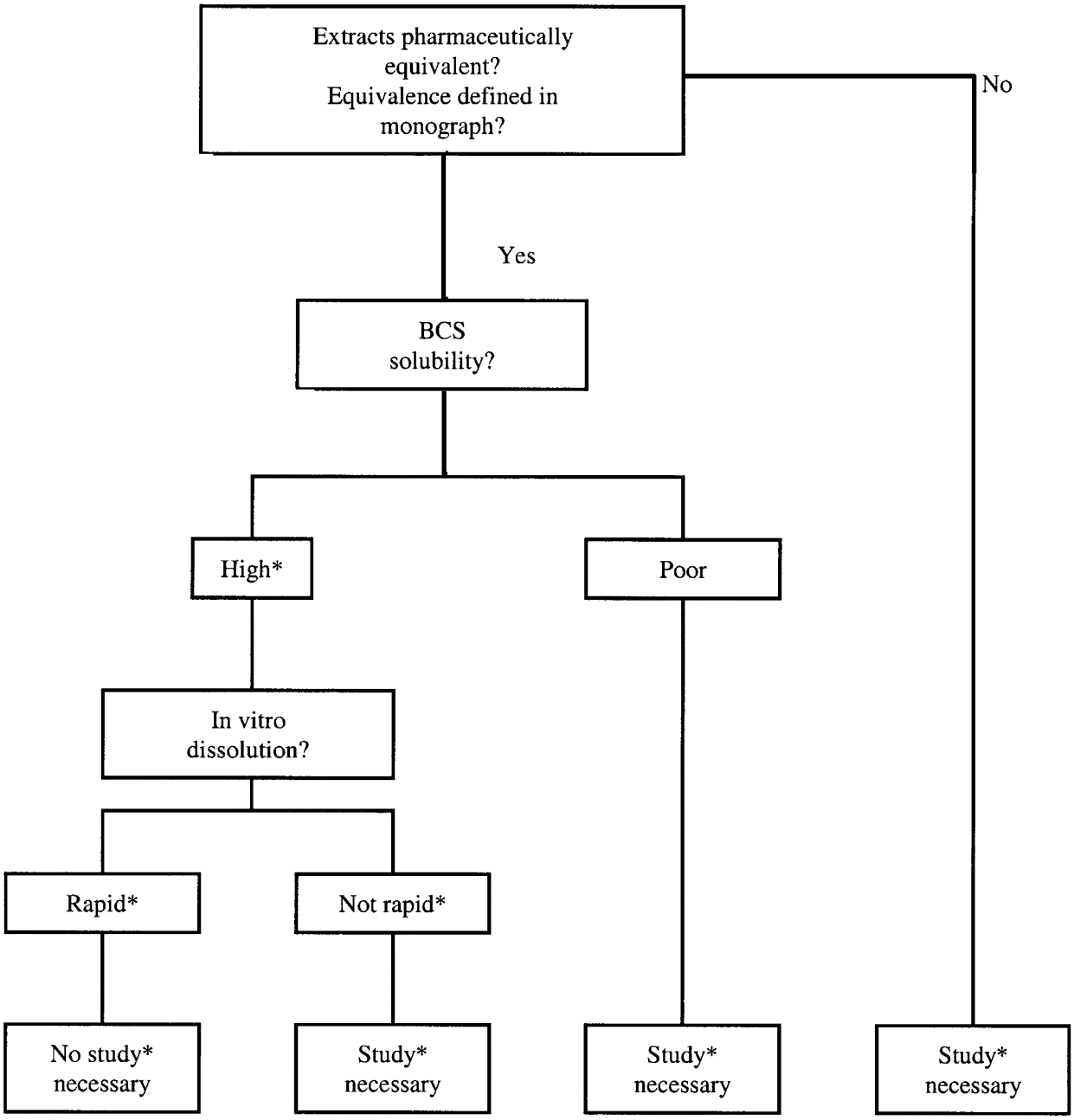
IMMEDIATE-RELEASE HMPs CONTAINING EXTRACTS FROM CLASS A

HMPs based on class A extracts are treated like chemically defined pharmaceutical products. In the case of substitution, the Note for Guidance on BA/BE should be fully considered. A waiver of bioequivalence studies may be considered under the conditions described in the Note for Guidance. This means that the active constituent(s) of the standardized extract should be completely soluble under physiological conditions and rapidly dissolved from the formulation ($\geq$85% at 15 min). If this is not the case, the similarity of the dissolution profiles between the test and reference products should be demonstrated.

IMMEDIATE-RELEASE HMPS CONTAINING EXTRACTS FROM CLASSES B AND C

In order to assess the therapeutical equivalence and the possibility of a substitution of HMPs, a decision tree may be applied involving three steps: pharmaceutical equivalence of extracts, their solubility, and dissolution from the formulations (see *Figure 1*). In the case of immediate-release HMPs containing class B or C extracts, the Note for Guidance on BA/BE in principle should be considered. An assessment should be made concerning the pharmaceutical equivalence of the extracts used in the test and reference formulations, their solubility under physiological conditions (>90%), and the dissolution profiles of active and/or lipophilic markers. If no markers are available in the case of class C extracts, the dissolution test may be dropped if no problems may be expected from the solubility characteristics of the extracts.

Fig. 1. Decision tree for class B and C extracts from the same plant



* Definitions: Note for Guidance

COMMENTS AND EXAMPLES

EXAMPLE HMPs BASED ON CLASS A EXTRACTS

This example involves formulations containing dry extracts of milk thistle (*Carduus marianus*). The reference product is a hard gelatin capsule containing a dry extract from milk thistle fruits and weighing 173–186.7 mg, corresponding to 140 mg silymarin (calculated as silibinin). The primary extraction solvent is ethyl acetate >97%. The DER is 36–44:1. The test product to be substituted for the reference product is a coated tablet containing dry extract from milk thistle fruits 170–200 mg, corresponding to 140 mg silymarin (calculated as silibinin). The primary extraction solvent is acetone. The DER is 35–45:1.

The milk thistle extracts in the test and reference product contain the same amount of silymarin as the active constituent and are pharmaceutically alternative. The solubility of milk thistle extracts and silymarin under physiological conditions is low. The pharmaceutical formulations are not pharmaceutically equivalent. A risk of bioinequivalence may be expected due to the differences in the solubility of the extracts and due to possible differences in the dissolution profiles of the pharmaceutical formulations. The requirements of the Note for Guidance are not fulfilled. BE studies, where relevant, are feasible for silymarin (*17*). Bioequivalence should be demonstrated by relevant studies or alternatively by unique clinical studies. The acceptance criteria for the silymarin dissolution rate should be specified for registration and routine control purposes for the marketed product.

EXAMPLE HMPs BASED ON CLASS B EXTRACTS

The first example involves formulations containing dry extracts of St. John's Wort (*Hypericum perforatum*). The reference product is a 300-mg coated tablet containing dry extract from St. John's Wort. The extraction solvent is methanol 80% (v/v). The DER is 4–7:1. The test product is a 425-mg hard gelatin capsule containing dry extract from St. John's Wort. The extraction solvent is methanol 60% (m/m). The DER is 3.5–6:1.

The reference and test product are not pharmaceutically equivalent regarding the extracts and the pharmaceutical formulations. The solubility of St. John's Wort extracts is >90% (see experimental data below). The known active (lipophilic) markers, hyperforin and hypericines, are not soluble under the BCS test conditions. The dissolution of the extracts and active markers is not rapid. The characteristics according to the Note for Guidance are not fulfilled. Bioanalytical examinations are feasible for hyperforin and hypericin (*18*, *19*). BA/BE studies with respect to those active markers are possible. Alternatively, clinical studies may be conducted with the test product. The specification for dissolution of active markers should be specified for registration and routine control purposes for the marketed product.

The second example involves formulations containing dry extracts of Valerian roots (*Valerianae officinalis*). The reference product is a 125-mg sugar-coated tablet containing Valerian root extract. The extraction solvent is ethanol 70% (v/v). The DER is 4–6.7:1. The test product is a 500-mg film-coated tablet containing Valerian root extract. The extraction solvent is ethanol 70% (v/v). The DER is 4–7:1.

The valerian extracts contained in the reference and test formulations may be regarded as pharmaceutically equivalent. Their solubility is high. Even in the high dose of 500 mg, the Valerian extract is soluble in all BCS buffers. If it can be shown that the extracts are rapidly dissolved from the formulation, bioequivalence or clinical studies may be waived.

EXPERIMENTAL DATA AND GUIDE FOR PRACTICAL ASPECTS OF SOLUBILITY TESTS

GENERAL CONDITIONS FOR THE DETERMINATION OF THE SOLUBILITY OF EXTRACTS AND ACTIVE MARKERS IN BCS BUFFERS

The general procedure for determining the solubility of extracts and active markers in BCS buffers involves determining the quantity of extract that remains after dissolving the highest strength of the product in 250 mL of solvents (buffers) I–III (I: pH 1.0; II: pH 4.6; III: pH 6.8; see reference *1*) at 37 °C. After stirring for 60 min the residues are filtered and gravimetrically determined after drying at 100 °C for 2 h. Because plant extracts often contain rather insoluble matrix components such as tannins, proteins, and other polymeric compounds assumed not to be linked to efficacy, extracts with a solubility of >90% are classified as very soluble. Extracts with a solubility >90% are classified as problematic. Active markers are also classified as problematic if their solubility from extracts is >90%.

EXAMPLE: CLASS A EXTRACT

This example involves formulations containing dry extracts of milk thistle (*Carduus marianus*). Milk thistle dry extract (200 mg) corresponding to the specification of the test product was dissolved in buffers I–III as described (see above). The solubility data obtained are listed in *Table 2*. The solubility data of silibinin were taken from literature (*20*). The data may be transferred to the solubility of silymarin. Because the data demonstrate solubility less than 30%, the requirements of BCS and the Note for Guidance are not fulfilled.

EXAMPLE: CLASS B EXTRACT

This example involves formulations containing dry extracts of St. John's Wort (*Hypericum perforatum*). St John's Wort dry extract (425 mg) corresponding to the specification of the reference product was dissolved in the buffers I–III as described (see above). The solubility data obtained are listed in *Table 3*.

EXAMPLE: CLASS C EXTRACT

This example concerns formulations containing dry extracts of Valerian root (*Valerianae officinalis*). Valerian root dry extract (500 mg) corresponding to the specification of

the reference product was dissolved in buffers I–III as described (see above). The solubility data are listed in *Table 4*. In every case the solubility criteria are fulfilled.

SUMMARY

Plant extracts can be classified according to one's knowledge of their composition and efficacy into 3 categories (A, B, and C). In the case of substitution of herbal medicinal products containing extracts from category A, the Note for Guidance on the Investigation of Bioavailability and Bioequivalence should fully be addressed. A waiver of bioequiv-
alence studies or clinical studies may be justified according to the Note for Guidance (particularly for products that show high solubility and rapid or similar dissolution).

In the case of HMPs containing class B or C extracts, the Note for Guidance on BA/BE in principle should be considered. An assessment should be made concerning pharmaceutical equivalence of the extracts used in the test and reference formulations, their solubility under physiological conditions (>90%), and the dissolution profile of active and/or lipophilic markers. If no markers are available in the case of class C extracts, the dissolution test may be dropped if no problems may be expected from the solubility characteristics of the extracts. A waiver of bioequivalence studies or clinical studies is possible if justified according to the Note for Guidance (in the case of products that display high solubility and rapid or similar dissolution in comparison to the reference product). The therapeutic equivalence of HMPs containing class B and C extracts in many instances may be demonstrated via clinical studies rather than by means of BE/BE studies.

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Table 1. Extract monographs of the European and the German Pharmacopoeias

European Pharmacopoeia	German Pharmacopoeia
Aloe dry extract, standardized (A)	Valerian root dry extract (C)
Buckthorn bark dry extract, standardized (A)	Ipecacuanha dry extract, standardized (A)
Senna leaf dry extract, standardized (A)	Rhubarb dry extract, standardized (A)
Belladonnae leaf dry extract, standardized (A)	Horse Chestnut seed dry extract, standardized (A)
St. John's Wort dry extract (B)*	Ginkgo dry extract (B)
	Milk thistle fruit dry extract, standardized (A)

* draft

Table 2

Solubility in	Buffer I	Buffer II	Buffer III
Milk thistle extract batch 1	18%	18%	25%
Milk thistle extract batch 2	24%	27%	30%
Silibinin at pH 7.4	8 mg/250 mL		

Table 3

Solubility in		Buffer I	Buffer II	Buffer III
Extracts with methanol 80%	batch 1	75%	94%	93%
	batch 2	71%	84%	91%
	batch 3	80%	93%	95%
Hyperforin (from extract)*		<250 µg/250 mL	2.5 mg/250 mL	7.5 mg/250 mL
Hypericines (from extract)*		<250 µg/250 mL	8 mg/250 mL	10 mg/250 mL

* Assuming that 425 mg St. John's Wort extract contains 0.85 mg hypericines (0.2%) and 8.5 mg hyperforine (2%), the requirements of BCS concerning high solubility are not fulfilled. Only in buffer III are the extracts highly soluble.

Table 4

Solubility in	Buffer I	Buffer II	Buffer III
Batch 1	97%	98%	99%
Batch 2	93%	90%	99%
Batch 3	96%	92%	95%

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

USP Dictionary of USAN and International Drug Names
2003 USP DICTIONARY SUPPLEMENT 2

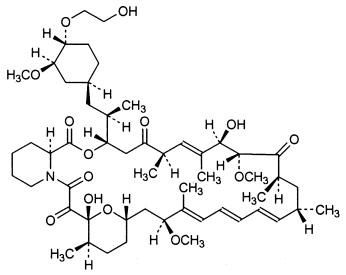
IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2003 edition of the USP Dictionary (USPD) up to date. The cumulative contents of the supplements to the current (2003) edition will be included in the next complete edition of the Dictionary.

New United States Adopted Names (USAN)

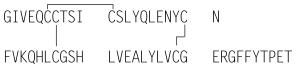
The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

Desmoteplase [*2003*] (des moe te′ plase). Plasminogen activator (Desmodus rotundus isoform α1 protein moiety reduced). Molecular weight is 55,000–58,000 daltons. *CAS-145137-38-8*. INN. *Treatment of acute myocardial infarction, acute ischemic stroke, pulmonary embolism and hemodialysis.* ✧*rDSPA alpha 1*

Everolimus [*2003*] (e ver oh′ li mus). $C_{53}H_{83}NO_{14}$. 958.25. (1) (1*R*,9*S*,12*S*,15*R*,16*E*,18*R*,19*R*,21*R*,23*S*,24*E*,26*E*,28*E*,30*S*,32*S*,35*R*)-1,18-Dihydroxy-12-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-19,30-dimethoxy-15,17,21,23,29,35-hexamethyl-11,36-dioxa-4-azatricyclo[30.3.1.0^{4,9}]hexatriaconta-16,24,26,28-tetraene-2,3,10,14,20-pentaone; (2) (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34,34a-Hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-(2-hydroxyethoxy)-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-*c*][1,4]oxaazacyclohentriacontine-1,5,11,28,29(4*H*,6*H*,31*H*)-pentone; (3) 42-*O*-(2-Hydroxyethyl)rapamycin. *CAS-159351-69-6*. INN. *Immunosuppressant.* (Novartis Pharma) ✧*RAD001*

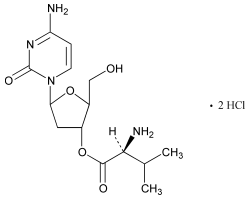


Insulin Glulisine [*2003*] (in′ soo lin gloo lis′ een). $C_{258}H_{384}N_{64}O_{78}S_6$. 5823. (1) Insulin (human),3^{B}-L-lysine,29^{B}-L-glutamic acid-; (2) [3^{B}-L-Lysine,29^{B}-L-glutamic acid]insulin (human). *CAS-207748-29-6*. INN. *Treatment of type 1 and type 2 diabetes.* (Aventis) ✧*HMR 1964*



Talizumab [*2003*] (tal iz′ ue mab). $C_{6518}H_{10020}N_{1728}O_{2036}S_{42}$. Immunoglobulin G, anti-(human immunoglobulin E Fc region) (human-mouse monoclonal Hu901 γ-chain), disulfide with human-mouse monoclonal Hu901 κ-chain, dimer. Molecular weight is approximately 146,348 daltons. *CAS-380610-22-0. Treatment to increase the threshold for peanut-induced anaphylaxis from unintended ingestion by those with peanut allergy.* ✧*TNX-901*

Valtorcitabine Dihydrochloride [*2003*] (val tore site′ ah been). $C_{14}H_{22}N_4O_5.2HCl$. 399.28. (1) L-Valine, 3′-ester with 2′-deoxycytidine, dihydrochloride; (2) 4-Amino-1-[3-*O*-[(2*S*)-2-amino-3-methylbutanoyl]-2-deoxy-β-D-*erythro*-pentofuranosyl]pyrimidin-2(1*H*)-one dihydrochloride. *CAS-359689-54-6. Antiviral; treatment of Hepatitis B.* ✧*NM-147*

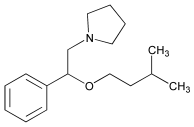


Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

Amixetrine

Change the chemical structure to read:



Carbomer 910

Change the name of the manufacturer of Carbopol 910 to read:

(Noveon).

Carbomer 934

Change the name of the manufacturer of Carbopol 934 to read:

(Noveon).

Carbomer 934P

Change the name of the manufacturer of Carbopol 934P and Carbopol 974P to read:

(Noveon).

Carbomer 940

Change the name of the manufacturer of Carbopol 940 and Carbopol 980 to read:

(Noveon).

Carbomer 941

Change the name of the manufacturer of Carbopol 941, Carbopol 981, and Carbopol 971P to read:

(Noveon).

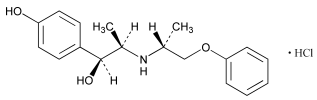
Carbomer 1342

Change the name of the manufacturer of Carbopol 1342, Pemulen TR-1, and Pemulen TR-2 to read:

(Noveon).

Isoxsuprine Hydrochloride

Change the chemical structure to read:



Octoxynol 9

Add the following brand name and manufacturer to read:

Triton X-100 (Union Carbide).

Phenoxybenzamine Hydrochloride

Change the name of the manufacturer to read:

(WellSpring Pharmaceutical Corporation).

Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Helath Organization (WHO).

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

Recommended International Nonproprietary Names

The following 46 nonproprietary names have been selected by the World Health Organization (WHO) as Recommended International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information*, Vol 16, No. 3, 2002.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Acolbifene	Efaproxiral	Lonafarnib	Peramivir
Asoprisnil	Fadolmidine	Lubazodone	Talibegron
Atomoxetine	Flindokalner	Luliconazole	Tariquidar
Bazedoxifene	Gimatecan	Meldonium	Tebanicline
Bifarcept	Icaridin	Metelimumab	Tecastemizole
Coluracetam	Iguratimod	Mitemcinal	Technetium (^{99m}Tc) Fanolesomab
Dapivirine	Illaprazole	Naxifylline	Tigecycline
Deferasirox	Indiplon	Oglufanide	Tiviciclovir
Degarelix	Indisulam	Olcegepant	Tosagestin
Dersalazine	Leconotide	Oregovomab	Trabectedin
Detiviciclovir	Licofelone	Otamixaban	Zosuquidar
Edonentan		Palifermin	

Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official *United States Pharmacopeia* or *National Formulary.* A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the *Federal Register* of February 1988.

> All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.

A formal procedure[1] is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all USANs for substances also named by the INN Committee are systematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.

A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.

Submissions to the USAN Council are expected to conform to the established Guiding Principles[2] and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable *category*, are separated by double spacing from the name(s) and *category* for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Suggested USAN	Category
Aclofarabine Baltarabine Clofarabine Colfarabine Crofarabine Eclofarabine Iclofarabine	*Treatment of primary refractory or relapsed acute myelogenous leukemia (AML) or acute lymphoblastic leukemia (ALL)*
Aclogrel Hydrochloride Cicloflugrel Hydrochloride Flosulagrel Hydrochloride Losulagrel Hydrochloride Prasulagrel Hydrochloride Prosulagrel Hydrochloride Prosulgrel Hydrochloride	*Platelet aggregation inhibitor*
Agaglitacor Atraglitazar Onaglitazar Optiglitacor Sivaglitazar Siviglitacor Sonaglitazar	*Antidiabetic*
Anretinib Arcutinib Palrotinib Panretinib Pelritinib Ramotinib Recetinib	*Antineoplastic*
Arabimodin Letaglitazar Maraglitazar Metabimodin Taraglitazar	*Treatment of type 2 diabetes mellitus, mixed dyslipidemia, atherosclerosis, and metabolic syndrome*
Arblurbifenil Arflurbifenil Arflurbifenpro Arflurbinifen Arflurbiprofen	*Antineoplastic*
Armodafinil	*Wake promoting agent*
Artofisopam	*Treatment of irritable bowel syndrome and Crohn's disease; antianxiety; antistress*

[1] *USP Dictionary of USAN and International Drug Names,* Preface.

[2] Ibid., Appendix VII.

Suggested USAN	Category
Balacipladib	*Treatment of pain and symptomatic management of arthritis*
Bicladib	
Ecocipladib	
Ecocladib	
Eficipladib	
Eicocladib	
Bectapitant Mesylate	
Vestipitant Mesylate	*Antiemetic*
Vintapitant Mesylate	
Bepisermin	*Antidiabetic*
Cobasermin	
Derasermin	
Obasermin	
Bitafosol Tetrasodium	*Treatment of rhinitis, URI, and lung disease, including cystic fibrosis; also retinal detachment and edema*
Denufosol Tetrasodium	
Dinufosol Tetrasodium	
Dipirafosol Tetrasodium	
Dipirfosol Tetrasodium	
Buntopitant Citrate	*Antiemetic*
Emepitant Citrate	
Galcopitant Citrate	
Lopitant Citrate	
Marpitant Citrate	
Muropitant Citrate	
Ripitant Citrate	
Tanopitant Citrate	
Capaprovir	*Treatment of Hepatitis C infection*
Cepaprovir	
Cepaprovirate	
Ciclocivirate	
Cicloprovirate	
Ciluprovir	
Carlizumab Pegol	*Treatment of rheumatoid arthritis and inflammatory bowel disease, specifically Crohn's disease*
Certolizumab Pegol	
Melizumab Pegol	
Midrolizumab Pegol	
Santulizimab Pegol	
Catelavancin Hydrochloride	*Antibacterial agent against Gram-positive pathogens*
Catellavancin Hydrochloride	
Selavancin Hydrochloride	
Stenavancin Hydrochloride	
Stenzenvancin Hydrochloride	
Telavancin Hydrochloride	
Ciclesonide	*Treatment of asthma as prophylactic therapy in adults and adolescents*
Delnostaurin Hydrochloride	*Antineoplastic*
Dionestaurin Hydrochloride	
Enzastaurin Hydrochloride	
Orapistaurin Hydrochloride	
Pirinostaurin Hydrochloride	
Dirlotapide	*Anti-obesity in dogs*
Edipatapide	
Eglumetad	*Treatment of anxiety and stress disorders*

Suggested USAN	Category
Enterointestinotrophin	*Treatment of intestinal diseases*
Gluglycatide	
Tediglucon	
Teduglutide	
Tegludutide	
Trodiglucon	
Purified Estrogens	*Hormone replacement therapy*
Sulfated Estrogens	
Synthetic Conjugated Estrogens, B	
Firosentan	*Antineoplastic*
Mendoentan	
Nobentan Potassium	
Pirosentan	
Poroentan Potassium	
Porosentan	
Human Secretin	*Diagnostic aid, specifically stimulation of pancreatic secretions*
Lumiliximab	*Treatment of allergic asthma, allergic rhinitis, chronic lymphocytic leukemia*
Riliximab	
Veriliximab	
Methylphenidate	*CNS stimulant*
Micafungin Sodium	*Intravenous treatment of fungal infections caused by Aspergillus and Candida species*
Miglustat	*Treatment of lipid storage diseases*
Mubritinib	*Antineoplastic*
Pavritinib	
Sardatinib	
Naprogecet	*Oral contraceptive*
Nosprogecet	
Panprogecet	
Paprogecet	
Pazprogecet	
Piprogecet	
Sanprogecet	
Sinprogecet	
Siprogecet	
Tanprogecet	
Nazaxaban	*Anticoagulant*
Razaxaban Hydrochloride	
Razoxaban	
Tozoxaban	
Zanaxaban	
Zoxaxaban	
Paclitaxel Conglutamex	*Anticancer therapy*
Paclitaxel Poliglutamex	
Parathormone (human recombinant)	*Treatment of osteoporosis*
Parathyroid Hormone (human recombinant)	
Parathyrotropin	

Suggested USAN	Category
Paroxetine Mesylate	*Treatment of major depressive disorder, obsessive compulsive disorder, and panic disorder*
Psyllium (hemicellulose) Psyllium Hemicellulose	*Laxation, cholesterol lowering*
Rafelagon Rafelreon Ramelreon Tafelgon Tafelreon Torelagon	*Treatment of sleep disorders*
Solabegron Hydrochloride	*Antidiabetic*
Testosterone Undecanoate	*Testosterone replacement therapy*
Tiplactinib Tiplactinin	*Treatment of fibrinolytic impairment*
Trabectedin	*Antineoplastic and antitumoral agent*
Undecanoate	*Radical; has been used in conjunction with testosterone, as testosterone undecanoate*
Xalaglumetad	*Treatment of anxiety and stress disorders*
Yttrium Y 90 Epratuzumab	*Radioimmunotherapy (RAIT) for non-Hodgkin's B-cell lymphoma patients*
Yttrium Y 90 Labetuzamab	*Radioimmunotherapy (RAIT) of CEA-expressing tumors in colorectal, pancreatic, lung, breast, ovarian, and medullary thyroid cancer*

Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable *category*, are separated by double spacing from the name(s) and *category* for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Nomenclature

Suggested INN	Category
Adaglen Jaocebrin Resevinadine	*Central benzodiazepine receptor (BZR) partial inverse agonist and a novel cognitive enhancer*
Adecatumumab Epcatumumab	*Treatment of Ep-CAM positive tumors*
Antithrombin Alfa Antithrombin Alfa (human) Antithrombin Alfa (recombinant)	*Anticoagulant*
Arblurbifenil	*Antineoplastic*
Artofisopam	*Treatment of irritable bowel syndrome, Crohn's disease, antianxiety, and antistress*
Celatopurone Emitobran Marcerion	*Mitochondrial benzodiazepine receptor (MBR)-selective agonist; anxiolytic and antidepressant agent*
Certolizumab Pegol	*Treatment of rheumatoid arthritis and inflammatory bowel disease; Crohn's disease*
Ciluprovir	*Treatment of Hepatitis C infection*
Clofarabine	*Treatment of primary refractory or relapsed acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL)*
Dobroxaban Flomerixaban Riveroxaban	*Prevention and treatment of thromboembolic disorders*
Doranidazole	*Hypoxic cell radiosensitizer*
Ecocipladib	*Treatment of pain and symptomatic management of arthritis*
Ecteinibin Ecteinoturbein Trabectedin Trantiblectein Turbinectein	*Antineoplastic*
Enzastaurin	*Antineoplastic*
Etomilast Tiamilast Tietomilast	*Phosphodiesterase IV inhibitor*
Histamine	*Injection treatment (in combination with interleukin-2) for the treatment of advanced metastatic melanoma with liver metastases*
Lumiliximab	*Treatment of allergic asthma, allergic rhinitis, chronic lymphocytic leukemia*
Maraglitazar	*Treatment of Type 2 diabetes, mixed dyslipidemia, atherosclerosis, and metabolic syndrome*
Marpitant Citrate	*Treatment and control of emesis*
Miglustat Miglutrastat	*Treatment of lipid storage diseases*
Mubritinib	*Treatment of cancer*
Nobentan	*Antineoplastic*
Obasermin	*HGF-1 hormone replacement used in the treatment of diabetes*
Osurtan Palasurtan Urosurtan	*Urotensin receptor antagonist for oral use in cardiovascular indications such as heart failure, hypertension, diabetes, and renal failure*

Suggested INN	Category
Paclitaxel Poliglutamex	*Anticancer therapy as a single agent or in combination with other anticancer therapies*
Parathyroid Hormone	*Treatment of osteoporosis*
Ramelreon	*Treatment of sleep disorders*
Razaxaban	*Anticoagulant; antithrombotic inhibitor of coagulant factor Xa*
Solabegron	*β-3 Adrenergic receptor agonist intended for use as an antidiabetic*
Sonaglitazar	*Antidiabetic; antidyslipidemic*
Tanprogecet	*Oral contraceptive*
Tegludutide	*Treatment of intestinal diseases*
Testosterone Undecanoate	Testosterone replacement therapy
Tiplactinin	*Treatment of fibrinolytic impairment diseases*
Undecanoate	*Radical; has been used in conjunction with testosterone, as testosterone undecanoate*
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INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 29(1).

[*Note—This index covers Vol. 29 No. 1, pp. 1–355, Vol. 29, No. 2 pp. 357–563, Vol. 29, No. 3 pp. 565–899, Vol. 29, No. 4 pp. 901–1362*]

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REFERENCE STANDARDS CATALOG

USING AND ORDERING USP REFERENCE STANDARDS

Official Reference Standards

USP Reference Standards are required for use in pharmacopeial assays and tests in the official standards publication, the *United States Pharmacopeia–National Formulary* (*USP–NF*). USP Reference Standards help to ensure compliance with the official, FDA-enforceable quality requirements in the *USP–NF*. The Reference Standards also lend themselves to many other applications, including measurements required to attain accurate and reproducible results in modern chromatographic and spectrophotometric methods.

Rigorous Testing and Quality Control

USP Reference Standards are selected for their high purity, critical characteristics, and suitability for the intended purpose. Unless a USP Reference Standard label states a specific potency or content, the USP Reference Standard is taken as being 100% pure for the USP purposes for which it is provided.

Heterogeneous substances, of natural origin, are also designated "Reference Standards" where needed. Usually these are the counterparts of international standards.

USP Reference Standards are established through a process of rigorous testing, evaluation, and quality control (See page 6 for a process overview). They are independently tested in three or more laboratories—USP, FDA, and academic and industrial laboratories throughout the United States. The Reference Standards are released under the authority of USP's Board of Trustees, on the recommendation of the USP Reference Standards Expert Committee, which approves selection and suitability of each lot.

Reference Standards Categories

USP offers more than 1,440 Reference Standards for pharmaceuticals, excipients, and dietary supplements. On pages 7–43 of this catalog, you'll find a full list of available USP and NF Reference Standards, with information updated through May 2003. The list includes:

- Reference Standards required by the current official edition of *USP–NF*.
- Reference Standards not required in the current *USP–NF*, but for which sufficient demand remains.
- Reference Standards specified in the current edition of the Food Chemicals Codex (FCC).
- Authentic Substances (AS)—highly purified samples of chemicals, including substances of abuse, required by analytical, clinical, pharmaceutical, and research laboratories.

The distribution of controlled substances is subject to the regulations and licensing provisions of the Drug Enforcement Administration (DEA) of the U.S. Department of Justice.

USP also collaborates with the World Health Organization in its program to provide international biological standards and chemical reference materials for antibiotics, biologicals, and chemotherapeutic agents. Some USP Reference Standards are standardized in terms of the corresponding international standards.

Proper Use of USP Reference Standards

USP Reference Standards are provided primarily for quality control use in conducting the pharmacopeial assays and tests described in the *USP–NF*. Neither Reference Standards nor Authentic Substances are intended for use as drugs, dietary supplements, or medical devices.

To serve its intended purpose, each USP Reference Standard must be properly stored, handled, and used. Users of USP Reference Standards should refer to General Chapter ⟨11⟩ in the *USP–NF*:

Listing and directions in USP–NF

- Refer to the list of revisions, additions, and deletions of individual USP Reference Standards in *USP 26–NF 21*. Individual *USP* or *NF* monographs specify the USP Reference Standard(s) required for assay and test procedures. The *USP 26–NF 21* General Test Chapter ⟨11⟩ USP Reference Standards provides additional information and instructions for proper use and storage. Note that if specific instructions for use appearing on the label of a USP Reference Standard differ from the instructions in Chapter ⟨11⟩, the instructions on the label take precedence.
- Consult the cumulative updates to Reference Standards information provided in *USP–NF Supplements* and also in *USP–NF* Interim Revision Announcements, which are published in USP's bimonthly journal, *Pharmacopeial Forum*.

Suitability for use

- The user must ascertain that the Reference Standards they are using are an official lot.
- The user must determine the suitability of Reference Standards for applications and uses not in the *USP–NF*.

USING AND ORDERING USP REFERENCE STANDARDS

Storing

- Ensure that the USP Reference Standards are stored in their original stoppered containers, according to any special label directions, away from heat and humidity, and protected from light.

Weighing

- Ensure that Reference Standard substances are accurately weighed—taking due account of relatively large errors potentially associated with weighing small masses—where it is directed that a standard solution or a standard preparation be prepared for a quantitative determination. See *USP 26–NF 21* General Chapters ⟨41⟩ *Weights and Balances* and ⟨31⟩ *Volumetric Apparatus*, and *USP–NF* General Notices, for information regarding appropriate use of USP Reference Standards.

Drying

- Use a clean and dry vessel, and not the original container, as the drying vessel where a USP Reference Standard is required to be dried before use.
- Make sure not to dry a specimen repeatedly at temperatures above 25 degrees.
- Follow any special drying requirements specified on the Reference Standards label or in specific sections of *USP* or *NF* monographs (note that any specific instructions on the label or in the monograph supersede the usual instructions in Procedures under Tests and Assays in *USP–NF* General Notices).
- Follow Method I under *USP–NF* General Chapter ⟨921⟩ *Water Determination* where the titrimetric determination of water is required at the time a Reference Standard is to be used. Instrumental or microanalytical methods are acceptable for this purpose. When using typical amounts, users must titrate about 50 mg of the Reference Standard with a fourfold dilution of the reagent.

ORDERING USP REFERENCE STANDARDS

Four convenient ways to order

1. Phone: Call USP with your requirements: (800) 227-8772 from the U.S. or Canada and (301) 881-0666 from other countries. Please note that DEA controlled substances cannot be placed over the phone.
   Hours of operation:
   Monday–Friday
   8:30AM–6:00PM
   Fax: Fax your orders to (301) 816-8148.
   Online: Order through the World Wide Web at http://www.usp.org/refstd. Please note that DEA controlled substances cannot be ordered online.
   Mail: Send all mail orders to:
   U.S. Pharmacopeia
   Customer Service Department
   12601 Twinbrook Parkway
   Rockville, MD 20852, USA

Important Order/Policy Information

For fax and mail orders, please use the order form at the back of this catalog. Official purchase orders on company letterhead may also be used to order USP Reference Standards. The purchase orders *must have billing and shipping addresses* and should include the catalog number, the name of the official Reference Standard, and the number of units ordered. Lot numbers need not be specified on written purchase orders as USP only ships current official lots. Confirmation orders may be sent and *must* clearly be designated as such. The USP does not assume responsibility for duplication of orders not clearly marked as confirmation orders.

Pricing

USP Reference Standards must be ordered in whole units. Please note that one unit may include several individual containers.

Reference Standards unit prices included in the product listings from pages 7–43 of this catalog are effective until December 31, 2003. Please note that prices and package sizes are subject to change without notice.

No Returns or Exchanges

USP Reference Standards may not be returned or exchanged for refund.

Quantity Discounts

A 5% discount is allowed for 5–24 units of any one Reference Standard in a single order, and a 10% discount for 25 or more units of any one Reference Standard in a single order. These discounts are subject to change without notice.

Shipping

- Reference Standards orders can only be shipped to a street address and not to P.O. boxes.
- Orders to the U.S. and Ontario, Canada are shipped via air courier of USP's choice at a charge of $11 or via air courier of the customer's choice at an additional $25 charge.
- Non-controlled substance orders to Canadian provinces other than Ontario are shipped via air courier of USP's choice at a

USING AND ORDERING USP REFERENCE STANDARDS

charge of U.S. $70. Carriers of the customer's choice incur an additional $25 charge.
- Non-controlled substance orders to be shipped outside the U.S. and Canada are accepted directly by USP only when customs forms related to export are not required. They are shipped via air courier of USP's choice at a charge of U.S. $70. Carriers of the customer's choice incur an additional $25 charge.
- Shipping in cold pack can be done at customer request for an extra charge of $25.
- Controlled substance orders to anywhere outside the U.S. are shipped via air courier of USP's choice with a charge of U.S. $220.
- An additional shipping charge may be assessed for dangerous goods shipments.
- An additional shipping charge of $75 will be assessed for rush/same-day shipments.
- Customers may provide their shipping account numbers to have shipping charged directly.

Payment
- Full payment in advance, in U.S. dollars, is required for all U.S. orders unless open account status has been granted by USP's Finance Department. To apply for open account status, an application can be requested by calling (301) 816-8177.
- Full payment in advance, in U.S. dollars, is required for all non-U.S. orders.
- Payment may be made by check, money orders, credit cards (VISA, MasterCard, American Express), and electronic wire transfer (please call (301) 816-8177 to get bank information for wire transfers). The customer is responsible for any bank fees and must include it in the payment. The customer is also responsible for any other fees such as customs duties, taxes, or tariffs.

List Chemicals

The following Reference Standards are ''List Chemicals'':

Dihydroergotamine Mesylate
[*]Ephedrine Sulfate
Ergonovine Maleate
Ergotamine Tartrate
Methylergonovine Maleate
Phenylpropanolamine Bitartrate
Phenylpropanolamine HCl
Pseudoephedrine HCl
Pseudoephedrine Sulfate

[*] Shipping this list chemical internationally requires a 15-day waiting period, but does not require an import permit.

An organization in the United States seeking to purchase a List Chemical Reference Standard for resale to another customer must have a DEA registration (either a controlled substance or List Chemical registration). If an organization in the United States is purchasing the List Chemical Reference Standard for its own analytical use, it must provide USP with a letter on company letterhead describing the reason for the purchase.

CONTROLLED DRUG SUBSTANCE ORDER

DEA Requirements (U.S. Orders)

For all orders for controlled drug substances—regulated by the U.S. Drug Enforcement Administration (DEA)—to be shipped within the U.S., a copy of the customer's current DEA Registration Certificate must be on file with USP. To order Schedule I and II standards, customers must submit, with their order forms or purchase orders, a DEA Form 222-C, properly completed. In addition, customers ordering DEA Schedules III and IV must provide appropriate DEA registration numbers for those schedules on their order forms or purchase orders.

DEA Requirements (International Orders)

For all international controlled drug substance orders, please contact Julie Smith at (301) 816-8164 or foreigncontrols@usp.org.

All orders for controlled drug substances-regulated by the U.S. Drug Enforcement Administration (DEA)-to be shipped outside the U.S. must be accompanied by:
1. Full payment.
2. An import permit (in English or with an English translation attached) valid at least 6 months from the date of its receipt by USP Customer Service.
3. A statement of non-reexport and use for medical or scientific purposes (in English or with an English translation attached).
4. Purchase Order or Price Quote given by USP.

On receiving the order, USP takes 2-3 business days to:
- Review all documents to make sure they are adequate and appropriate.
- Complete and legally approve the required DEA forms.
- Forward the forms to the DEA office to obtain the necessary Export Permits.

USING AND ORDERING USP REFERENCE STANDARDS

USP cannot ship items without an Export Permit. While it typically takes 6–10 weeks to get the permit from the DEA, USP has no control over the time in which permits are issued. On receiving the Export Permit, USP completes processing of the order in 1–3 days and ships out the materials through its freight forwarder.

Controlled substances (CI, CII, CIII, CIV, CV) shipped to an international address, including Canada, add $25 per unit.

For controlled substance orders to be shipped to Mexico, in addition to the DEA processing period, an additional week is required to obtain a certificate from the Mexican Embassy, authorizing the shipment to enter the country. Customers will pay an additional $114 to cover the fee charged by the Mexican Embassy per import permit.

Back Orders

USP will ship a back-ordered item if that item becomes available within 30 days of the date the order is placed if there is a valid open P.O. or payment for the item. If the order is more than 30 days old when the item becomes available, the customer will receive a Notice of Availability (NOA), indicating that the item is available. Such items will be shipped only after USP receives written authorization by the customer. The order will be canceled if the Reference Standard does not become available within six months of the original order. NOAs not replied to within 45 days of generation will be cancelled, and the customer account will be credited appropriately.

Customers may send confirmation orders for back-ordered Reference Standards that subsequently become available. They must clearly designate the confirmation orders as such—USP is not responsible for duplication of orders not clearly designated.

HOW TO READ PRODUCT LISTINGS

Column 1 (Catalog Number): Catalog number currently assigned to each Reference Standard and Authentic Substance. ***Please include this number in your orders.***

Column 2 (Former Catalog Number): Catalog numbers assigned prior to July 2002. These numbers are provided for your convenience so you can easily cross-reference current numbers against your earlier orders.

Column 3 (Description): Product description as designated in *USP–NF*, the product label, and / or the Drug Enforcement Administration Control Schedule, as applicable. The quantity of material per container follows the name in parentheses (all materials are in single containers unless otherwise specified).

Column 4 (Current Lot): Current lot designation of each ***official*** item being distributed as of the date of this catalog. If the current lot is blank, the item is not in distribution.

Column 5 (Change Code): Codes that identify any change in USP Reference Standards status or information since the **May/June 2003,** official Catalog. Code interpretations are as follows:

Change Code	Interpretation
1	New Reference Standard
2	New lot
3	Change in package size or description
4	Correction of typographical error
5	New catalog number—use for all orders
6	Previous lot no longer official; only current lot to be used
7	Valid use date of previous lot extended
8	Change in catalog number and / or name, see cross-reference section
9	Discontinued

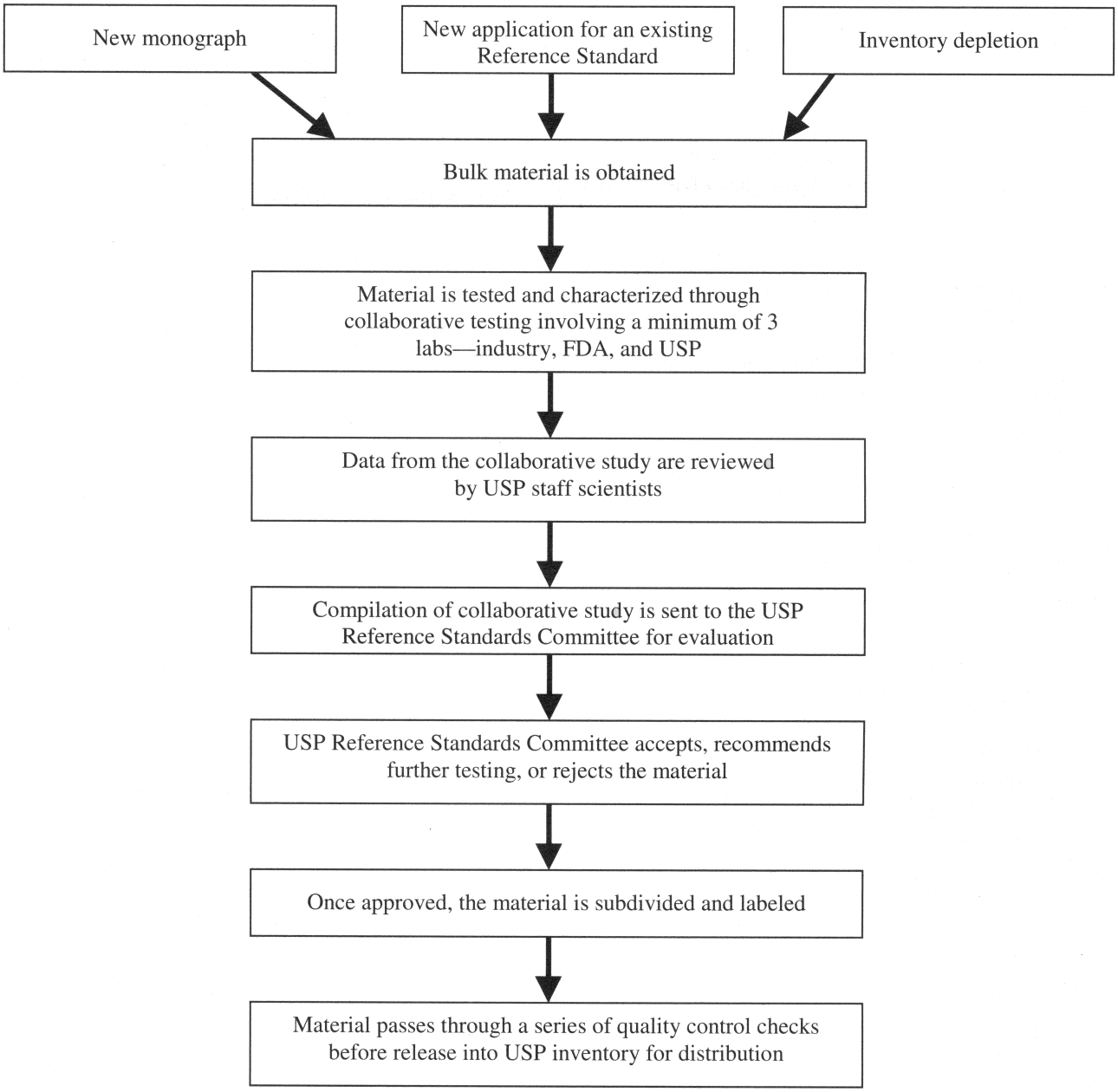
Column 6 (Previous Lot/Valid Use Date): Identifies lots no longer being distributed. The indicated month and in parenthesis indicates the date (last day of the month) through which that lot was valid as an official USP Reference Standard. (e.g. "F-1 (06/00)" means lot F-1 is no longer being distributed, but was considered official through June 30, 2000.)

Column 7 (CAS Number)*: Chemical Abstracts Service number, when available, for USP Reference Standards and Authentic Substances. In case of mixtures, typically, the CAS number of the analyte of interest is listed.

Column 8 (Price) lists the price of the reference standard.

* CAS numbers are provided for informational purposes only and their listing in the USP Reference Standards Catalog does not indicate official designation of any CAS number to a salt, isomer, hydration state, or other chemical form of any specific Reference Standard or Authentic Substance.

DEVELOPMENT PROCESS FOR USP STANDARDS



USP Reference Standards and Authentic Substances

Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1000601	00060-1	Acebutolol Hydrochloride (125 mg)	F-1			[34381-68-5]	$150
1001003	00100-3	Acenocoumarol (200 mg)	F			[152-72-7]	$150
1001502	00150-2	Acepromazine Maleate (250 mg)	F-2		F-1 (05/02)	[3598-37-6]	$150
1002505		Acesulfame Potassium (200 mg)	F0C136	1		[55589-62-3]	$250
1003009	00300-9	Acetaminophen (400 mg)	J-1		J (05/02) I (05/99)	[103-90-2]	$119
1004001	00400-1	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)	L		K (02/00)	[103-84-4]	$72
1005004	00500-4	Acetazolamide (2 g)	J			[59-66-5]	$150
1006007	00600-7	Acetohexamide (250 mg)	H		G-1 (06/99)	[968-81-0]	$150
1006506	00650-6	Acetohydroxamic Acid (200 mg)	F-1		F (03/03)	[546-88-3]	$150
1007000	00700-0	Acetophenazine Maleate (200 mg)	F-1			[5714-00-1]	$150
1008002	00800-2	alpha-d-2-Acetoxy-4-dimethylamino-1,2-diphenyl-3-methylbutane (125 mg)	G-3			n/f	$468
1008501	00850-1	Acetylcholine Chloride (200 mg)	G			[60-31-1]	$150
1009005	00900-5	Acetylcysteine (200 mg)	H1B169		H (01/04)	[616-91-1]	$150
1009901	00990-1	Acetyltributyl Citrate (500 mg)	F			[77-90-7]	$150
1009923	00992-3	Acetyltriethyl Citrate (500 mg)	F-1		F (05/02)	[77-89-4]	$150
1012065	01206-5	Acyclovir (300 mg)	I			[59277-89-3]	$189
1012101	01210-1	Adenine (200 mg)	G-1		G (6/00)	[73-24-5]	$150
1012123	01212-3	Adenosine (200 mg)	F1B058		F (04/03)	[58-61-7]	$150
1012145	01214-5	Agigenin (25 mg)	F			n/f	$150
1012509	01250-9	L-Alanine (200 mg)	F-2		F-1 (04/01)	[56-41-7]	$150
1012553	01255-3	Albendazole (200 mg)	G		F-1 (01/00)	[54965-21-8]	$150
1012600	01260-0	Albuterol (200 mg)	I		H (12/00)	[18559-94-9]	$150
1012633	01263-3	Albuterol Sulfate (200 mg)	J		I (04/00)	[51022-70-9]	$150
1012757	01275-7	Alclometasone Dipropionate (300 mg)	H		G (01/00)	[66734-13-2]	$150
1012780		Alendronate Sodium (200 mg)	F0B315			[121268-17-5]	$150
1012906	01290-6	Alfentanil Hydrochloride **CII** (500 mg)	F0B016			[70879-28-6]	$199
1012939		Allantoin (200 mg)	F0C169	1		[97-59-6]	$150
1012950	01295-0	Alliin (25 mg)	F			[556-27-4]	$1,466
1013002	01300-2	Allopurinol (250 mg)	I-1		I (07/02)	[315-30-0]	$150
1013024	01302-4	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)	G		F-3 (05/02) F-2 (04/99)	n/f	$468
1013057	01305-7	S-Allyl-L-Cysteine (25 mg)	F			n/f	$468
1014005	01400-5	Alphaprodine Hydrochloride **CII** (250 mg)	F			[561-78-4]	$199
1015008	01500-8	Alprazolam **CIV** (200 mg)	H			[28981-97-7]	$199
1016000	01600-0	Alprostadil (25 mg)	H			[745-65-3]	$1,466
1017105	01710-5	Altretamine (500 mg)	F			[645-05-6]	$150
1017502	01750-2	Dried Aluminum Hydroxide Gel (200 mg)	F2B120		F-1 (01/04)	[21645-51-2]	$150
1018505	01850-5	Amantadine Hydrochloride (200 mg)	H		G (04/01)	[665-66-7]	$150
1019202	01920-2	Amcinonide (200 mg)	G0B260		F-1 (03/04)	[51022-69-6]	$150
1019417		Amifostine Disulfide (25 mg)	F0C152	1		[112901-68-5]	$468
1019508	01950-8	Amikacin (200 mg)	I		H (08/00)	[37517-28-5]	$150
1019701	01970-1	Amiloride Hydrochloride (500 mg)	H			[17440-83-4]	$150
1019756	01975-6	Aminobenzoate Potassium (200 mg)	F-1		F (06/01)	[138-84-1]	$150
1019767	01976-7	Aminobenzoate Sodium (200 mg)	F			[55-06-6]	$150
1019803	01980-3	Aminobenzoic Acid (200 mg) (p-aminobenzoic acid)	H		G (10/00)	[150-13-0]	$150
1020008	02000-8	Aminobutanol (500 mg)	G-1		G (06/99)	[13054-87-0]	$374

USP Reference Standards and Authentic Substances

Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1021000	02100-0	Aminocaproic Acid (200 mg)	F-4			[60-32-2]	$150
1021703	02170-3	N-(Aminocarbonyl)-N-[([5-nitro-2-furanyl]-methylene)-amino]-glycine (25 mg)	F-1			n/f	$468
1022808	02280-8	2-Amino-5-chlorobenzophenone (25 mg)	I		H-1 (01/03)	[719-59-5]	$468
1023403	02340-3	3-Amino-6-chloro-1-methyl-4-phenylcarbostyril (25 mg)	I		H (04/01)	[5220-02-0]	$468
1025205	02520-5	Aminoglutethimide (200 mg)	F			[125-84-8]	$150
1025307	02530-7	m-Aminoglutethimide (100 mg)	G		F (05/01)	n/f	$468
1025351	02535-1	Aminohippuric Acid (200 mg)	F-1			[61-78-9]	$150
1025806	02580-6	2-[3-Amino-5-(n-methylacetamido)-2,4,6-triiodobenzamido]-2-deoxy-d-glucose (25 mg)	F			n/f	$468
1025908		Aminopentamide Sulfate (200 mg)	F0B273			[60-46-8]	$150
1026004	02600-4	m-Aminophenol (300 mg)	F			[591-27-5]	$468
1026401	02640-1	Aminosalicylic Acid (125 mg)	F-1		F (03/99)	[65-49-6]	$119
1026605	02660-5	3-Amino-2,4,6-triiodobenzoic Acid (50 mg)	G			[3119-15-1]	$468
1027007	02700-7	5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid (50 mg)	F-1			[2280-89-9]	$468
1028000		Amitraz (200 mg)	F0C042			[33089-61-1]	$150
1029002	02900-2	Amitriptyline Hydrochloride (200 mg)	J0A004		I (03/03)	[549-18-8]	$150
1029909	02990-9	Ammonio Methacrylate Copolymer Type A (100 mg)	F-1		F (06/01)	[33434-24-1]	$150
1029910	02991-0	Ammonio Methacrylate Copolymer Type B (100 mg)	F-1		F (05/00)	[33434-24-1]	$150
1029953		Ammonium Chloride (200 mg)	F0C134	1		[12125-02-9]	$150
1030001	03000-1	Amobarbital **CII** (200 mg)	F-2			[57-43-2]	$199
1031004	03100-4	Amodiaquine Hydrochloride (500 mg)	H0B238		G-1 (04/03)	[6398-98-7]	$150
1031401	03140-1	Amoxapine (200 mg)	G		F-1 (04/02)	[14028-44-5]	$150
1031503	03150-3	Amoxicillin (200 mg)	I			[61336-70-7]	$150
1032007	03200-7	Amphotericin B (125 mg)	J-2		J-1 (07/02)	[1397-89-3]	$119
1033000	03300-0	Ampicillin (Anhydrous) (200 mg)	J-1		J (12/01)	[69-53-4]	$150
1033203	03320-3	Ampicillin Sodium (125 mg)	G-1		G (10/99)	[69-52-3]	$119
1033407	03340-7	Ampicillin (Trihydrate) (200 mg)	G			[7177-48-2]	$150
1034002	03400-2	Amprolium (200 mg)	F-1		F (04/02)	[121-25-5]	$150
1034308	03430-8	Amrinone (500 mg)	G			[60719-84-8]	$150
1034320	03432-0	Amrinone Related Compound A (100 mg) (5-carboxamide[3,4'-bipyridin]-6(1H)-one)	F			[62749-46-6]	$468
1034341	03434-1	Amrinone Related Compound B (100 mg) (N-(1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-yl)-2-hydroxypropanamide)	F-1		F (03/00)	n/f	$468
1034363	03436-3	Amrinone Related Compound C (50 mg) (1,6-dihydro-6-oxo-(3,4'-bipyridine)-5-carbonitrile)	F-1		F (05/00)	n/f	$468
1036008	03600-8	Anileridine Hydrochloride **CII** (250 mg)	F			[126-12-5]	$199
1036507	03650-7	3-Anilino-2-(3,4,5-trimethoxybenzyl) acrylonitrile (25 mg)	G-1			[30078-48-9]	$468
1038003	03800-3	Antazoline Phosphate (200 mg)	H		G-1 (04/02)	[154-68-7]	$150
1039006	03900-6	Anthralin (200 mg)	I0B221		H (11/02)	[1143-38-0]	$150
1040005	04000-5	Antipyrine (200 mg)	G		F-4 (09/01)	[60-80-0]	$150
1040708	04070-8	Apigenin-7-glucoside (30 mg)	F			n/f	$468
1041008	04100-8	Apomorphine Hydrochloride (250 mg)	H		G (01/03)	[41372-20-7]	$156
1041609	04160-9	Apraclonidine Hydrochloride (100 mg)	H0B112		G (06/03)	[73218-79-8]	$461
1042000	04200-0	Aprobarbital **CIII** (200 mg) (AS)	F-1			[77-02-1]	$199
1042500	04250-0	L-Arginine (200 mg)	G-1		G (09/00)	[74-79-3]	$150
1042601	04260-1	Arginine Hydrochloride (125 mg)	G0B060		F-1 (05/03)	[1119-34-2]	$119
1042703	04270-3	Arsanilic Acid (25 mg)	F			[98-50-0]	$150
1043003	04300-3	Ascorbic Acid (1 g) (Vitamin C)	Q0B012		P (04/03)	[50-81-7]	$150

USP Reference Standards and Authentic Substances

Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1043706	04370-6	Aspartame (200 mg)	H1B125		H (05/03)	[22839-47-0]	$150
1043750		Aspartame Acesulfame (200 mg)	F0C137	1		[106372-55-8]	$150
1043728	04372-8	Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid)	H		G-1 (10/99)	[5262-10-2]	$468
1043819	04381-9	Aspartic Acid (100 mg)	F0B087			[6899-03-2]	$150
1044006	04400-6	Aspirin (500 mg)	H		G-1 (11/02)	[50-78-2]	$150
1044301	04430-1	Astemizole (200 mg)	F			[68844-77-9]	$150
1044403	04440-3	Atenolol (200 mg)	H		G (08/01)	[29122-68-7]	$150
1044651		Atovaquone (200 mg)	F0B190			[95233-18-4]	$150
1044662		Atovaquone Related Compound A (25 mg) (cis-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthoquinone)	F0B188			n/f	$468
1044800		Atracurium Besylate (100 mg)	F0B143			[64228-81-5]	$150
1045009	04500-9	Atropine Sulfate (500 mg)	M0B098		L-2 (04/03) L-1 (06/02) L (10/00)	[5908-99-6]	$150
1045337	04533-7	Avobenzone (500 mg)	G0B280		F (09/03)	[70356-09-1]	$150
1045508	04550-8	Aurothioglucose (100 mg)	H0B224		G (10/03) F (12/01)	[12192-57-3]	$150
1045600	04560-0	Azaerythromycin A (100 mg)	G		F-1 (02/02) F (02/99)	[76801-85-9]	$150
1045756	04575-6	Azaperone (200 mg)	F			[1649-18-9]	$150
1045803	04580-3	Azatadine Maleate (200 mg)	G0B300	2	F-1 (04/04) F (06/00)	[3978-86-7]	$150
1046001	04600-1	Azathioprine (200 mg)	H		G-1 (02/00)	[446-86-6]	$150
1046056	04605-6	Azithromycin (100 mg)	G		F (06/00)	[117772-70-0]	$150
1046103	04610-3	Azlocillin Sodium (200 mg)	F			[37091-65-9]	$150
1046147	04614-7	Azo-aminoglutethimide (100 mg)	F			n/f	$468
1046205	04620-5	Aztreonam (200 mg)	G0C077	2	F-1 (03/04)	[78110-38-0]	$150
1046307	04630-7	Aztreonam E-isomer (50 mg)	F			n/f	$150
1046409	04640-9	Open Ring Aztreonam (50 mg)	F			[87500-74-1]	$150
1047300	04730-0	Bacampicillin Hydrochloride (200 mg)	G0B053		F (11/02)	[37661-08-8]	$150
1047503	04750-3	Bacitracin (1 g) (Susceptibility disk standard)	G			[1405-87-4]	$150
1048007	04800-7	Bacitracin Zinc (200 mg)	N0A024		M-1 (11/02) M (02/00)	[1405-89-6]	$150
1048200	04820-0	Baclofen (500 mg)	I			[1134-47-0]	$150
1048222	04822-2	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)	H			n/f	$374
1048506	04850-6	Beclomethasone Dipropionate (200 mg)	K		J (12/00)	[5534-09-8]	$150
1049000	04900-0	Bendroflumethiazide (200 mg)	G-1			[73-48-3]	$150
1050009	05000-9	Benoxinate Hydrochloride (200 mg)	F-2		F-1 (10/99)	[5987-82-6]	$119
1051001	05100-1	Benzalkonium Chloride (5 mL of approx. 10% aqueous solution)	K0B151		J (06/03)	[8001-54-5]	$150
1054000	05400-0	Benzocaine (500 mg)	I			[94-09-7]	$150
1055002	05500-2	Benzoic Acid (300 mg)	F6B173	2	F-5 (03/04) F-4 (07/01)	[65-85-0]	$150
1056005	05600-5	Benzonatate (1 g)	I0B003		H (01/03)	[104-31-4]	$150
1056504	05650-4	1,4-Benzoquinone (200 mg)	G1B145		G (01/04) F-1 (11/01) F (09/00)	[106-51-4]	$150
1057507	05750-7	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)	H0B069		G-4 (03/03)	[121-30-2]	$468

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1059003	05900-3	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F-1			[5411-22-3]	$199
1060002	06000-2	Benzthiazide (200 mg)	F			[91-33-8]	$150
1061005	06100-5	Benztropine Mesylate (200 mg)	H			[132-17-2]	$150
1061901	06190-1	Benzyl Alcohol (500 mg/ampule)	G0B306		F0B106 (10/03)	[100-51-6]	$150
1062008	06200-8	Benzyl Benzoate (5 g)	J0C060	2	I (05/04)	[120-51-4]	$150
1064003	06400-3	1-Benzyl-3-methyl-5-aminopyrazole Hydrochloride (25 mg)	F-1			[59-63-2]	$468
1065006	06500-6	Bephenium Hydroxynaphthoate (500 mg)	F			[3818-50-6]	$150
1065618		Betahistine Hydrochloride (200 mg)	F0C105	1		[5579-84-0]	$150
1065709	06570-9	Betaine Hydrochloride (200 mg)	F-1		F (11/02)	[590-46-5]	$150
1066009	06600-9	Betamethasone (200 mg)	K-1		K (11/02)	[378-44-9]	$150
1067001	06700-1	Betamethasone Acetate (500 mg)	J0B079		I (08/03)	[987-24-6]	$150
1067307	06730-7	Betamethasone Benzoate (200 mg)	F-1			[22298-29-9]	$150
1067704	06770-4	Betamethasone Dipropionate (125 mg)			J (04/04) I (03/99)	[5593-20-4]	$119
1068004	06800-4	Betamethasone Sodium Phosphate (500 mg)	J0B043		I-1 (02/03) I (01/01)	[151-73-5]	$150
1069007	06900-7	Betamethasone Valerate (200 mg)	J		I (05/00)	[2152-44-5]	$150
1069903	06990-3	Betaxolol Hydrochloride (200 mg)	G		F-1 (06/00)	[63659-19-8]	$150
1070006	07000-6	Betazole Hydrochloride (200 mg)	H			[138-92-1]	$150
1071009	07100-9	Bethanechol Chloride (200 mg)	G		F-3 (07/01)	[590-63-6]	$150
1071304	07130-4	Bile Salts (10 g) (Sodium Taurocholate)	H-1		H (05/99)	[145-42-6]	$119
1071508	07150-8	Biotin (200 mg)	H1B019		H (04/03)	[58-85-5]	$150
1072001	07200-1	Biperiden (200 mg)	F2B080		F-1 (02/04)	[514-65-8]	$150
1073004	07300-4	Biperiden Hydrochloride (200 mg)	F-3		F-2 (06/99)	[1235-82-1]	$150
1074007	07400-7	Bisacodyl (125 mg)	I1B162		I (01/04) H-1 (02/99)	[603-50-9]	$119
1074700	07470-0	2,5-Bis(D-arabino-1,2,3,4-tetrahydroxybutyl)pyrazine (25 mg)	F			n/f	$468
1075203	07520-3	Bis(2-ethylhexyl)maleate (250 mg)	F-2		F-1 (01/01)	[142-16-5]	$468
1075509	07550-9	p-Bis(di-n-propyl)carbamylbenzenesulfonamide (50 mg)	F			[57-66-9]	$468
1075531	07553-1	Bismuth Citrate (100 mg)	F			[813-93-4]	$150
1075553	07555-3	Bismuth Subsalicylate (100 mg)	F			[14882-18-9]	$150
1075757	07575-7	Bisoprolol Fumarate (200 mg)	F0B038			[104344-23-2]	$150
1076002	07600-2	4,4'-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone (25 mg)			G (05/03)	n/f	$468
1076308	07630-8	Bleomycin Sulfate (15 mg)	J0B213		I (01/04)	[9041-93-4]	$295
1076352	07635-2	Bretylium Tosylate (200 mg)	F-1			[61-75-6]	$150
1076363		Brinzolamide (200 mg)	F0C034			[138890-62-7]	$150
1076374		Brinzolamide Related Compound A (50 mg) ((S)-(-)-4-ethylamino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide)	F0C033			n/f	$468
1076385		Brinzolamide Related Compound B (50 mg) ((R)-4-amino-2,3-dihydro-2-(3-methoxypropyl)-4H-thieno-[3,2,e]-thiazine-6-sulfonamide-1,1-dioxide ethanedioate)	F0C035			n/f	$468
1076501	07650-1	Bromocriptine Mesylate (150 mg)	I			[22260-51-1]	$150
1077005	07700-5	Bromodiphenhydramine Hydrochloride (200 mg)	F-1			[1808-12-4]	$150
1077708	07770-8	8-Bromotheophylline (400 mg)	G		F (07/02)	[10381-75-6]	$150
1078008	07800-8	Brompheniramine Maleate (125 mg)	I1A036		I (01/03) H-1 (04/99)	[980-71-2]	$119
1078303	07830-3	Bumetanide (250 mg)	H0B030		G (03/03)	[28395-03-1]	$150

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1078325	07832-5	Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)	F-2		F-1 (05/00)	n/f	$468
1078336	07833-6	Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid)	F-2		F-1 (01/03)	[28328-53-2]	$468
1078507	07850-7	Bupivacaine Hydrochloride (1 g)	H		G-2 (03/03) G-1 (08/02)	[14252-80-3]	$150
1078700	07870-0	Buprenorphine Hydrochloride **CIII** (50 mg)	F-1		F (02/99)	[53152-21-9]	$199
1078711	07871-1	Buprenorphine Related Compound A (50 mg) (21-[3-(1-propenyl)]-7-alpha-[(S)-1-hydroxy-1,2,2-trimethylpropyl]-6,14-endo-ethano-6,7,8,14-tetrahydrooripavine)	F1C076	2	F (04/04)	n/f	$468
1078733		Bupropion (200 mg)	F0C123	1		[31677-93-7]	$200
1078802	07880-2	Buspirone Hydrochloride (200 mg)	G			[33386-08-2]	$150
1079000	07900-0	Butabarbital **CIII** (200 mg)	H0C007	2	G (03/04)	[125-40-6]	$199
1080000	08000-0	Butacaine Sulfate (600 mg)	F			[149-15-5]	$150
1081002	08100-2	Butalbital **CIII** (200 mg)	G2B077		G-2 (06/03) G (05/02)	[77-26-9]	$199
1081501	08150-1	Butamben (200 mg)	F			[94-25-7]	$150
1082300	08230-0	Butoconazole Nitrate (200 mg)	F1B097		F (03/03)	[64872-77-1]	$150
1082504	08250-4	Butorphanol Tartrate **CIV** (500 mg)	J		I (06/00)	[58786-99-5]	$199
1082800	08280-0	Monotertiary-butyl-p-benzoquinone (100 mg) (FCC)	F			[3602-55-9]	$150
1082901	08290-1	Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate (25 mg)	F-1			n/f	$468
1083008	08300-8	2-*tert*-Butyl-4-hydroxyanisole (200 mg)	L0C028		K (09/03)	[88-32-4]	$150
1083100	08310-0	3-*tert*-Butyl-4-hydroxyanisole (200 mg)	J		I-1 (09/01)	[121-00-6]	$150
1084000	08400-0	Butylparaben (200 mg)	I0C139	2	H-1 (03/04) H (09/01)	[94-26-8]	$150
1085003	08500-3	Caffeine (200 mg)	J		I (06/02)	[58-08-2]	$150
1086006	08600-6	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)	J0B204	7	I (03/04)	[58-08-2]	$88
1086108	08610-8	Calcifediol (75 mg)	G			[63283-36-3]	$150
1086356	08635-6	Calcium Ascorbate (200 mg)	F-1		F (08/01)	[5743-28-2]	$150
1086800	08680-0	Calcium Gluceptate (200 mg)	F-1		F (09/00)	[29039-00-7]	$150
1086902	08690-2	Calcium Lactobionate (200 mg)	G0B138		F-1 (01/04) F (11/01)	[110638-68-1]	$150
1087009	08700-9	Calcium Pantothenate (200 mg) (Vitamin B5)	N-1		N (06/00)	[137-08-6]	$150
1087202	08720-2	Calcium Saccharate (200 mg)	F			[5793-89-5]	$150
1088001	08800-1	Candicidin (200 mg)	F			[1403-17-4]	$150
1089004	08900-4	Cannabidiol **CI** (25 mg) (AS)	F-2			[13956-29-1]	$199
1090003	09000-3	Cannabinol **CI** (25 mg) (AS)			F-2 (05/02)	[521-35-7]	$199
1091006	09100-6	Capreomycin Sulfate (200 mg)	G		F (06/01)	[1405-37-4]	$150
1091108	09110-8	Capsaicin (100 mg)	G-1		G (03/02) F-1 (06/00) F (03/99)	[404-86-4]	$150
1091200	09120-0	Captopril (200 mg)	H			[62571-86-2]	$150
1091221	09122-1	Captopril Disulfide (100 mg)	G1B066		G (01/04)	[64806-05-9]	$468
1092009	09200-9	Carbachol (200 mg)	G			[51-83-2]	$150
1093001	09300-1	Carbamazepine (100 mg)	J		I-1 (02/00)	[298-46-4]	$150
1093205	09320-5	Carbarsone (200 mg)	F			[121-59-5]	$150
1093500	09350-0	Carbenicillin Indanyl Sodium (300 mg)	G			[26605-69-6]	$150
1094004	09400-4	Carbenicillin Monosodium Monohydrate (200 mg)	G-2			n/f	$150
1095506	09550-6	Carbidopa (400 mg)	I		H (10/99)	[38821-49-7]	$150

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1095517		Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)	H0B121		G (04/03)	n/f	$468
1096000	09600-0	Carbinoxamine Maleate (200 mg)	H		G-1 (11/02)	[3505-38-2]	$150
1096407	09640-7	Carboplatin (100 mg)	G		F (03/00)	[41575-94-4]	$153
1096509	09650-9	Carboprost Tromethamine (25 mg)	F-1		F (02/01)	[58551-69-2]	$468
1096600	09660-0	Carisoprodol (1 g)	G		F-2 (05/02)	[78-44-4]	$150
1096757	09675-7	Carteolol Hydrochloride (200 mg)	F-1		F (11/00)	[51781-21-6]	$150
1096804	09680-4	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I			[76333-53-4]	$538
1096906	09690-6	Cefaclor (400 mg)	H			[70356-03-5]	$150
1096917	09691-7	Cefaclor, Delta-3-Isomer (30 mg)	G		F-1 (02/00)	n/f	$150
1097104	09710-4	Cefadroxil (125 mg)	I		H (04/99)	[66592-87-8]	$119
1097308	09730-8	Cefamandole Lithium (200 mg)	H			n/f	$150
1097400	09740-0	Cefamandole Nafate (200 mg)	H			[42540-40-9]	$150
1097501	09750-1	Cefamandole Sodium (250 mg)	F			[30034-03-8]	$150
1097603	09760-3	Cefazolin (400 mg)	K		J (06/00)	[25953-19-9]	$150
1097636		Cefepime Hydrochloride (500 mg)	F0C063	1		[123171-59-5]	$150
1097647		Cefepime Hydrochloride System Suitability (25 mg)	F0C095	1		n/f	$150
1097658	09765-8	Cefixime (500 mg)	F			[79350-37-1]	$150
1097771	09777-1	Cefmenoxime Hydrochloride (350 mg)	F			[75738-58-8]	$150
1097782	09778-2	Cefmetazole (200 mg)	F-1		F (04/02)	[56796-20-4]	$150
1097750	09775-0	Cefonicid Sodium (1 g)	G			[61270-78-8]	$150
1097705	09770-5	Cefoperazone Dihydrate (200 mg)	H		G (12/99)	[62893-19-0]	$150
1097807	09780-7	Ceforanide (200 mg)	F-1		F (07/00)	[60925-61-3]	$150
1097909	09790-9	Cefotaxime Sodium (250 mg)	I			[64485-93-4]	$119
1097975	09797-5	Cefotetan (500 mg)	G		F (09/00)	[69712-56-7]	$150
1098005	09800-5	Cefotiam Hydrochloride (325 mg)	G0B050		F (01/03)	[66309-69-1]	$150
1098049	09804-9	Cefprozil E-Isomer (50 mg)	F-1		F (05/01)	[121123-17-9]	$150
1098050	09805-0	Cefprozil Z-Isomer (200 mg)	G0C037		F (12/03)	[121123-17-9]	$150
1098107	09810-7	Cefoxitin (500 mg)	I		H (05/00)	[35607-66-0]	$150
1098129	09812-9	Ceftazidime, Delta-3-Isomer (25 mg)	G		F (03/00)	n/f	$200
1098130	09813-0	Ceftazidime Pentahydrate (300 mg)	H		G (12/99)	[78439-06-2]	$150
1098173	09817-3	Ceftizoxime (200 mg)	H			[68401-81-0]	$150
1098184	09818-4	Ceftriaxone Sodium (350 mg)	G0B264		F (08/03)	[104376-79-6]	$150
1098195	09819-5	Ceftriaxone Sodium E-Isomer (25 mg)	H		G (08/01) F-1 (02/00)	n/f	$200
1098209	09820-9	Cefuroxime Sodium (200 mg)	H		G-1 (05/00)	[56238-63-2]	$150
1098220	09822-0	Cefuroxime Axetil (500 mg)	G		F-1 (05/02)	[64544-07-6]	$150
1098231	09823-1	Cefuroxime Axetil Delta-3-Isomers (35 mg)	H0B160		G (03/03)	n/f	$150
1098300	09830-0	Cellulose Acetate (125 mg)	F-1		F (11/99)	[9004-35-7]	$119
1098355	09835-5	Cellulose Acetate Phthalate (125 mg)	F-1		F (03/99)	[9004-38-0]	$119
1098708	09870-8	Cephaeline Hydrobromide (200 mg)	G-1			n/f	$468
1099008	09900-8	Cephalexin (250 mg)	I-2		I-1 (03/00)	[23325-78-2]	$150
1102000	10200-0	Cephalothin Sodium (200 mg)	I			[58-71-9]	$150
1102408	10240-8	Cephapirin Benzathine (100 mg)	F			[97468-37-6]	$150
1102500	10250-0	Cephapirin Sodium (200 mg)	I-1		I (07/02)	[24356-60-3]	$150
1102805	10280-5	Cephradine (200 mg)	J		I (04/00)	[58456-86-3]	$150
1103003	10300-3	Cetyl Alcohol (100 mg)	I		H (03/99)	[36653-82-4]	$150
1103105		Cetyl Palmitate (50 mg)	F0B241			[540-10-3]	$150

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1104006	10400-6	Cetylpyridinium Chloride (500 mg)	I		H-1 (06/01) H (08/99)	[6004-24-6]	$150
1106001	10600-1	Chlorambucil (125 mg)	G		F-1 (02/99)	[305-03-3]	$119
1107004	10700-4	Chloramphenicol (200 mg)	N		M (03/00)	[56-75-7]	$150
1107300	10730-0	Chloramphenicol Palmitate (200 mg)	G-1			[530-43-8]	$150
1107401	10740-1	Chloramphenicol Palmitate Nonpolymorph A (200 mg)	F-1			[530-43-8]	$468
1107503	10750-3	Chloramphenicol Palmitate Polymorph A (200 mg)	G		F (08/99)	[530-43-8]	$468
1109000	10900-0	Chlordiazepoxide **CIV** (200 mg)	I0B063		H-1 (03/03)	[58-25-3]	$199
1110009	11000-9	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4			[438-41-5]	$199
1110020	11002-0	Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide)	G			[963-39-3]	$468
1112503	11250-3	Chlorobutanol (200 mg)	G		F-3 (12/01)	[6001-64-5]	$150
1115556	11555-6	beta-Chlorogenin (20 mg)	F			n/f	$150
1117008	11700-8	Chloroprocaine Hydrochloride (200 mg)	G0B285		F-3 (01/04) F-2 (03/99)	[3858-89-7]	$150
1118000	11800-0	Chloroquine Phosphate (500 mg)	I		H (10/99)	[50-63-5]	$150
1119309	11930-9	4'-Chloro-3'-sulfamoyl-2-benzophenone Carboxylic Acid (100 mg)	F-3			n/f	$468
1121005	12100-5	Chlorothiazide (200 mg)	H0B161		G (04/03)	[58-94-6]	$150
1122008	12200-8	Chlorotrianisene (1 g)	F			[569-57-3]	$150
1122700	12270-0	Chloroxylenol (125 mg)	F-1		F (10/99)	[88-04-0]	$119
1122722	12272-2	Chloroxylenol Related Compound A (50 mg) (2-chloro-3,5-dimethylphenol)	F-1			[5538-41-0]	$468
1123000	12300-0	Chlorpheniramine Maleate (125 mg)	M0B020		L-1 (06/03)	[113-92-8]	$119
1123102	12310-2	Chlorpheniramine Maleate Extended-Release Tablets (Drug Release Calibrator, Single Unit) (60 Tablets)	G0B259		F (06/03)	[113-92-8]	$150
1124003	12400-3	Chlorphenoxamine Hydrochloride (200 mg)	F-1			[562-09-4]	$150
1125006	12500-6	Chlorpromazine Hydrochloride (200 mg)	J		I (04/99)	[69-09-0]	$150
1126009	12600-9	Chlorpropamide (200 mg)	H			[94-20-2]	$150
1127001	12700-1	Chlorprothixene (200 mg)	F-1			[113-59-7]	$150
1129007	12900-7	Chlortetracycline Hydrochloride (200 mg)	J-1		J (02/02)	[64-72-2]	$150
1130006	13000-6	Chlorthalidone (125 mg)	H-1		H (07/99)	[77-36-1]	$119
1130505	13050-5	Chlorzoxazone (500 mg)	I		H (07/01)	[95-25-0]	$150
1130527	13052-7	Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol)	G-1		G (11/00)	[95-85-2]	$468
1131009	13100-9	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157		L (10/03) K (09/99)	[67-97-0]	$153
1131803	13180-3	Delta-4,6-cholestadienol (30 mg)	F			[14214-69-8]	$150
1132001	13200-1	Cholesteryl Caprylate (200 mg)	F			[1182-42-9]	$150
1133004	13300-4	Cholestyramine Resin (500 mg)	I			[11041-12-6]	$119
1133503	13350-3	Cholic Acid (2 g) (AS)	F3B159		F-2 (01/03)	[81-25-4]	$150
1133536		Choline Bitartrate (200 mg)	F0C057	1		[87-67-2]	$150
1133570		Chondroitin Sulfate Sodium (300 mg)	F0B256			[39455-18-0]	$150
1133638	13363-8	Chromium Picolinate (100 mg)	F			[14639-25-9]	$150
1134007	13400-7	Chymotrypsin (300 mg)	I		H (06/01)	[9004-07-3]	$150
1134030	13403-0	Ciclopirox Olamine (125 mg)			G (05/03)	[41621-49-2]	$119
1134051	13405-1	Cilastatin Ammonium Salt (100 mg)	F-1		F (07/00)	n/f	$150
1134062	13406-2	Cimetidine (200 mg)	I			[51481-61-9]	$150
1134073	13407-3	Cimetidine Hydrochloride (200 mg)	F			[70059-30-2]	$150
1134109	13410-9	Cinoxacin (200 mg)	F			[28657-80-9]	$150

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1134313	13431-3	Ciprofloxacin (125 mg)	G-1		G (05/01)	[85721-33-1]	$119
1134324	13432-4	Ciprofloxacin Ethylenediamine Analog (25 mg)	J0A030		I (01/03) H-1 (02/99)	n/f	$200
1134335	13433-5	Ciprofloxacin Hydrochloride (400 mg)	H		G (04/00)	[86393-32-0]	$150
1134357	13435-7	Cisplatin (100 mg)	H		G (03/01)	[15663-27-1]	$150
1134368	13436-8	Citric Acid (200 mg)	F1B092		F-1 (01/04) F (07/02)	[77-92-9]	$150
1134379	13437-9	Clarithromycin (75 mg)	F4B183		F-3 (01/04) F-2 (09/01)	[81103-11-9]	$150
1134380	13438-0	Clarithromycin Related Compound A (50 mg) (6,11-di-O-methylerythromycin A)	G		F (04/01)	n/f	$200
1134404	13440-4	Clavam-2-carboxylate Potassium (1 Pellet)			G0B225 (12/03) F (10/03)	n/f	$468
1134426	13442-6	Clavulanate Lithium (200 mg)	I		H (09/02)	n/f	$150
1134506	13450-6	Clemastine Fumarate (250 mg)	I		H (10/00)	[14976-57-9]	$150
1135000	13500-0	Clidinium Bromide (2 g)	G			[3485-62-9]	$150
1135021	13502-1	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)	I			[76201-95-1]	$468
1136002	13600-2	Clindamycin Hydrochloride (200 mg)	G4A017		G-3 (07/03) G-2 (05/99)	[58207-19-5]	$412
1137005	13700-5	Clindamycin Palmitate Hydrochloride (200 mg)	F-2			[25507-04-4]	$412
1138008	13800-8	Clindamycin Phosphate (125 mg)	I0C165	2	H-3 (04/04) H-2 (07/03) H-1 (02/99)	[24729-96-2]	$206
1138201	13820-1	Clioquinol (500 mg)	M		L-1 (01/03)	[130-26-7]	$150
1138405	13840-5	Clobetasol Propionate (200 mg)	F-1		F (10/01)	[25122-46-7]	$150
1138427	13842-7	Clobetasol Propionate Related Compound A (50 mg) (9-alpha-fluoro-11-beta-hydroxy-16-beta-methyl-3-oxo-androsta-1,4-diene-17(R)-spiro-2'-[4'-chloro-5'-ethylfuran-3'(2'H)-one])	F-1		F (01/03)	n/f	$200
1138507	13850-7	Clocortolone Pivalate (200 mg)	G			[34097-16-0]	$150
1138904	13890-4	Clofazimine (200 mg)	F			[2030-63-9]	$150
1139000	13900-0	Clofibrate (1 g)	I		H (04/01)	[637-07-0]	$150
1140000	14000-0	Clomiphene Citrate (500 mg)	H		G-1 (10/99)	[50-41-9]	$150
1140101	14010-1	Clomiphene Related Compound A (100 mg) ((E,Z)-2-[4-(1,2-diphenylethenyl)phenoxy]-N,N-diethylethanamine Hydrochloride)	F1B206		F (09/03)	n/f	$200
1140305	14030-5	Clonazepam **CIV** (200 mg)	G1B175		G (01/04) F-2 (01/00)	[1622-61-3]	$199
1140327	14032-7	Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril)	G2B110		G-1 (01/04) G (02/99)	n/f	$468
1140338	14033-8	Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone)	H		G (04/01)	[2011-66-7]	$468
1140407	14040-7	Clonidine Hydrochloride (200 mg)	G			[4205-91-8]	$150
1140509	14050-9	Clorazepate Dipotassium **CIV** (125 mg)	G0B027		F-1 (06/03) F (12/99)	[57109-90-7]	$199
1140702	14070-2	Clorsulon (200 mg)	F1B084		F (01/04)	[60200-06-8]	$150
1141002	14100-2	Clotrimazole (200 mg)	J		I (05/99)	[23593-75-1]	$119
1141024	14102-4	Clotrimazole Related Compound A (25 mg) ((o-chlorophenyl)diphenylmethanol)	I		H (10/01) G-1 (02/99)	[66774-02-5]	$468
1141909	14190-9	Cloxacillin Benzathine (200 mg)	F-1		F (03/02)	[23736-58-5]	$150
1142005	14200-5	Cloxacillin Sodium (200 mg)	L0B086		K (01/04)	[7081-44-9]	$150

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1142107		Clozapine (100 mg)	F0C032			[5786-21-0]	$250
1143008	14300-8	Cocaine Hydrochloride **CII** (250 mg)	I0B074		H-2 (01/04) H-1 (02/99)	[53-21-4]	$199
1143802	14380-2	Codeine N-Oxide **CI** (50 mg)	G0A034		F-1 (11/02)	[3688-65-1]	$199
1144000	14400-0	Codeine Phosphate **CII** (100 mg)	I-1		I (09/02) H-1 (01/00)	[41444-62-6]	$199
1145003	14500-3	Codeine Sulfate **CII** (250 mg)	H-2		H-1 (01/02)	[6854-40-6]	$199
1146006	14600-6	Colchicine (300 mg)	J		I (05/02)	[64-86-8]	$150
1146505	14650-5	Colestipol Hydrochloride (200 mg)	F-1			[37296-80-3]	$150
1147009	14700-9	Colistimethate Sodium (200 mg)	H			[8068-28-8]	$150
1148001	14800-1	Colistin Sulfate (200 mg)	G-1		G (09/99)	[1264-72-8]	$150
1149004	14900-4	Corticotropin (5.6 Units/vial; 5 vials)	M		L (06/99)	[9002-60-2]	$119
1150003	15000-3	Cortisone Acetate (150 mg)	I			[50-04-4]	$150
1150353	15035-3	Creatinine (100 mg)	F			[60-27-5]	$150
1150502	15050-2	Cromolyn Sodium (500 mg)	J		I (06/00)	[15826-37-6]	$150
1150706	15070-6	Crospovidone (200 mg)	G			[9003-39-8]	$150
1151006	15100-6	Crotamiton (200 mg)	H-1		H (07/00)	[483-63-6]	$150
1152009	15200-9	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N		M-3 (08/99)	[68-19-9]	$150
1152508	15250-8	Cyclacillin (200 mg)	G			[3485-14-1]	$150
1153001	15300-1	Cyclizine (1 g)			F (04/04)	[82-92-8]	$150
1154004	15400-4	Cyclizine Hydrochloride (200 mg)	G			[303-25-3]	$150
1154503	15450-3	Cyclobenzaprine Hydrochloride (200 mg)	G0A013		F-3 (07/03)	[6202-23-9]	$150
1154558	15455-8	Alpha Cyclodextrin (50 mg)	F-1		F (10/00)	[10016-20-3]	$150
1154569	15456-9	Beta Cyclodextrin (250 mg)	G		F-1 (12/02)	[7585-39-9]	$150
1154707	15470-7	Cyclomethicone 4 (200 mg)	F-2		F-1 (06/02)	[69430-24-6]	$150
1154809	15480-9	Cyclomethicone 5 (125 mg)	F-2		F-1 (09/99)	[69430-24-6]	$119
1154900	15490-0	Cyclomethicone 6 (200 mg)	F2B024		F-1 (03/03)	[69430-24-6]	$150
1156000	15600-0	Cyclopentolate Hydrochloride (300 mg)	H		G (04/00)	[5870-29-1]	$150
1157002	15700-2	Cyclophosphamide (500 mg)	J			[6055-19-2]	$119
1157501	15750-1	2-Cyclopropylmethylamino-5-chlorobenzophenone (50 mg)	F			[2955-38-6]	$468
1158005	15800-5	Cycloserine (200 mg)	G			[68-41-7]	$150
1158504	15850-4	Cyclosporine (50 mg)	H-1		H (11/02) G-2 (03/00)	[59865-13-3]	$461
1158650	15865-0	Cyclosporine Resolution Mixture (25 mg)	F			[108027-45-8] (U)	$396
1159008	15900-8	Cyclothiazide (200 mg)	F-1			[2259-96-3]	$150
1161000	16100-0	Cyproheptadine Hydrochloride (500 mg)	G		F-4 (11/02)	[41354-29-4]	$150
1161509	16150-9	L-Cysteine Hydrochloride (200 mg)	H		G (05/00)	[7048-04-6]	$150
1162002	16200-2	Cytarabine (250 mg)	G-2		G-1 (07/00)	[147-94-4]	$150
1162308	16230-8	Dacarbazine (125 mg)	H		G (01/99)	[4342-03-4]	$119
1162320	16232-0	Dacarbazine Related Compound A (50 mg) (5-aminoimidazole-4-carboxamide Hydrochloride)	G	2	G (03/04) F (03/00)	[72-40-2]	$468
1162330	16233-0	Dacarbazine Related Compound B (100 mg) (2-azahypoxanthine)	F-1		F (12/01)	[63907-29-9]	$468
1162400	16240-0	Dactinomycin (50 mg)	I			[50-76-0]	$411
1162501	16250-1	Danazol (200 mg)	H		G (10/00)	[17230-88-5]	$150
1164008	16400-8	Dapsone (125 mg)	G-3		G-2 (08/99)	[80-08-0]	$119
1164700	16470-0	Daunorubicin Hydrochloride (200 mg)	L0B307		K (11/03) J (08/00)	[23541-50-6]	$461

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1165000	16500-0	Decamethonium Bromide (250 mg)	F			[541-22-0]	$150
1166003	16600-3	Deferoxamine Mesylate (500 mg)	I			[138-14-7]	$150
1166309	16630-9	Dehydroacetic Acid (200 mg)	F			[520-45-6]	$150
1166400	16640-0	Dehydrocarteolol Hydrochloride (100 mg)	F			n/f	$468
1166502	16650-2	Dehydrocholic Acid (200 mg)	F			[81-23-2]	$150
1169001	16900-1	Demecarium Bromide (250 mg)	F			[56-94-0]	$150
1170000	17000-0	Demeclocycline Hydrochloride (200 mg)	H		G-1 (08/01)	[64-73-3]	$150
1171003	17100-3	Denatonium Benzoate (200 mg)	I0B129		H (09/02)	[86398-53-0]	$150
1171706	17170-6	Desacetyl Diltiazem Hydrochloride (50 mg)	I		H (08/00)	[23515-45-9]	$468
1172006	17200-6	Desipramine Hydrochloride (125 mg)	H-1		H (10/99)	[58-28-6]	$119
1173009	17300-9	Deslanoside (100 mg)	H-1			[17598-65-1]	$150
1173235		Desogestrel (50 mg)	F0B282			[54024-22-5]	$150
1173246		Desogestrel Related Compound A (15 mg) (13-Ethyl-11-methylene-18, 19-dinor-5alpha, 17alpha-preg-3-en-20-yl-17-ol, desogestrel delta-3 isomer)	F0B279			n/f	$468
1173257		Desogestrel Related Compound B (15 mg) (3-Hydroxy-desogestrel)	F0B284			n/f	$468
1173268		Desogestrel Related Compound C (25 mg) (3-Keto-desogestrel)	F0B281			[54048-10-1]	$468
1173508	17350-8	Desoximetasone (200 mg)	H0B036		G (01/04)	[382-67-2]	$150
1174001	17400-1	Desoxycorticosterone Acetate (200 mg)	J0C014		I (01/04) H (05/00)	[56-47-3]	$150
1175004	17500-4	Desoxycorticosterone Pivalate (125 mg)			G (01/04)	[808-48-0]	$119
1176007	17600-7	Dexamethasone (125 mg)	J			[50-02-2]	$119
1176506	17650-6	Dexamethasone Acetate (200 mg)	G		F-1 (06/99)	[55812-90-3]	$150
1177000	17700-0	Dexamethasone Phosphate (200 mg)	J1B070		J (08/03) I (03/00)	[312-93-6]	$150
1178002	17800-2	Dexbrompheniramine Maleate (200 mg)	J		I (03/03)	[2391-03-9]	$150
1179005	17900-5	Dexchlorpheniramine Maleate (500 mg)	G1A025		G (12/02)	[2438-32-6]	$150
1179504	17950-4	Dexpanthenol (500 mg)	I		H (02/02)	[81-13-0]	$154
1179854		Dextran 4 Calibration (100 mg)	F0C002			[9004-54-0]	$150
1179865		Dextran 10 Calibration (100 mg)	F0C010			[9004-54-0]	$150
1179876		Dextran 40 Calibration (100 mg)	F0C011			[9004-54-0]	$150
1179720		Dextran 40 System Suitability (200 mg)	F0B181			[9004-54-0]	$150
1179887		Dextran 70 Calibration (100 mg)	F0C013			[9004-54-0]	$150
1179763		Dextran 70 System Suitability (200 mg)	F0B182			[9004-54-0]	$150
1179898		Dextran 250 Calibration (100 mg)	F0C039			[9004-54-0]	$150
1179800		Dextran Vo Marker (100 mg)	F0B242			[9004-54-0]	$150
1180004	18000-4	Dextroamphetamine Sulfate **CII** (500 mg)	H		G (08/03) F-6 (12/99)	[51-63-8]	$208
1180503	18050-3	Dextromethorphan (2 g)	H		G (06/00)	[125-71-3]	$468
1181007	18100-7	Dextromethorphan Hydrobromide (500 mg)	J0B167		I (07/03)	[6700-34-1]	$150
1181302	18130-2	Dextrose (500 mg)	J-1		J (11/02) I (08/99)	[50-99-7]	$119
1181506	18150-6	Diacetylated Monoglycerides (200 mg)	G			[68990-54-5]	$150
1182000	18200-0	Diacetylfluorescein (200 mg)	H		G (01/02)	[596-09-8]	$150
1183002	18300-2	Diacetylmorphine Hydrochloride **CI** (25 mg) **(AS)** (Heroin Hydrochloride)	J		I-1 (10/99)	[1502-95-0]	$199
1184005	18400-5	Diatrizoic Acid (100 mg)	G			[50978-11-5]	$150

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1184027	18402-7	Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid)	I		H (02/00)	[1713-07-1]	$468
1185008	18500-8	Diazepam **CIV** (100 mg)	I		H (12/01)	[439-14-5]	$199
1185020	18502-0	Diazepam Related Compound A (25 mg) (2-Methyl-amino-5-chlorobenzophenone)	I		H-1 (11/02) H (04/00)	[1022-13-5]	$468
1186000	18600-0	Diazoxide (200 mg)	G1C017		G (12/03)	[364-98-7]	$150
1187003	18700-3	Dibucaine Hydrochloride (200 mg)	I		H-2 (01/03)	[61-12-1]	$150
1187207	18720-7	Dichloralphenazone **CIV** (200 mg)	F0B010			[480-30-8]	$199
1188006	18800-6	Dichlorphenamide (200 mg)	G-1			[120-97-8]	$150
1188800	18880-0	Diclofenac Sodium (200 mg)	H0B150	2	G-1 (03/04) G (05/01)	[15307-79-6]	$150
1188811	18881-1	Diclofenac Related Compound A (100 mg) (N-(2,6-dichlorophenyl)indolin-2-one)	H		G (05/02)	[15362-40-0]	$471
1189009	18900-9	Dicloxacillin Sodium (500 mg)	I0B142		H (05/03)	[13412-64-1]	$150
1190008	19000-8	Dicumarol (200 mg)	G			[66-76-2]	$150
1191000	19100-0	Dicyclomine Hydrochloride (125 mg)	H		G (03/99)	[67-92-5]	$119
1192003	19200-3	Dienestrol (125 mg)	I			[84-17-3]	$119
1193006	19300-6	Diethylcarbamazine Citrate (200 mg)	G-1			[1642-54-2]	$150
1193301	19330-1	Diethylene Glycol Monoethyl Ether (0.5 mL/ampule)	F0B095			[111-90-0]	$150
1193505	19350-5	Diethyl Phthalate (200 mg)	G		F-1 (03/00)	[84-66-2]	$150
1194009	19400-9	Diethylpropion Hydrochloride **CIV** (200 mg)	H			[134-80-5]	$199
1195001	19500-1	Diethylstilbestrol (200 mg)	K-4			[56-53-1]	$150
1197007	19700-7	Diethyltoluamide (3 g)	H			[134-62-3]	$119
1197302	19730-2	Diflorasone Diacetate (200 mg)	G		F-1 (03/00)	[33564-31-7]	$150
1197506	19750-6	Diflunisal (200 mg)	G			[22494-42-4]	$150
1198000	19800-0	Digitalis (3 g)	F			[8031-42-3]	$150
1199002	19900-2	Digitoxin (200 mg)	M			[71-63-6]	$150
1200000	20000-0	Digoxin (250 mg)	O0B096		N-1 (04/03)	[20830-75-5]	$150
1200600	20060-0	Dihydrocapsaicin (25 mg)	G0C071	3	F-1 (12/03) F (01/00)	[19408-84-5]	$150
1200804	20080-4	Dihydrocodeine Bitartrate **CII** (200 mg)	H		G (03/01)	[5965-13-9]	$199
1201002	20100-2	17alpha-Dihydroequilin (50 mg)	H			[6639-99-2]	$200
1202005	20200-5	Dihydroergotamine Mesylate (250 mg) **(List Chemical)**	J0B085		I (03/03)	[6190-39-2]	$150
1203008	20300-8	Dihydrostreptomycin Sulfate (200 mg)	J			[5490-27-7]	$150
1204000	20400-0	Dihydrotachysterol (30 mg/ampule; 4 ampules)	I			[67-96-9]	$150
1204102	20410-2	Dihydroxyacetone (250 mg)	F			[96-26-4]	$150
1204805		Diloxanide Furoate (200 mg)	F0C026			[3736-81-0]	$150
1205003	20500-3	Diltiazem Hydrochloride (200 mg)	I			[33286-22-5]	$150
1206006	20600-6	Dimenhydrinate (100 mg)	J0B055		I (06/03)	[523-87-5]	$150
1208001	20800-1	Dimethisoquin Hydrochloride (2 g)	G			[2773-92-4]	$150
1210105	21010-5	N-(3-Dimethylamino-propyl)-2-aza-8,8-diethyl-8-germaspiro [4:5]decane-1,3-dione (AS)	F			[41992-23-8]	$150
1211006	21100-6	Dimethyl Sulfoxide (3 g)	F-3		F-2 (05/02)	[67-68-5]	$150
1213001	21300-1	Dinoprost Tromethamine (50 mg)	F			[38562-01-5]	$1,466
1213103		Dinoprostone (50 mg)	F0C030			[363-24-6]	$1,466
1214004	21400-4	Dioxybenzone (150 mg)	F1B277		F (10/03)	[131-53-3]	$150
1216000	21600-0	Diphemanil Methylsulfate (500 mg)	H			[62-97-5]	$150
1217909	21790-9	Diphenhydramine Citrate (125 mg)	H0B128		G (04/03)	[88637-37-0]	$119
1218005	21800-5	Diphenhydramine Hydrochloride (200 mg)	J0B013		I (07/03)	[147-24-0]	$150
1219008	21900-8	Diphenoxylate Hydrochloride **CII** (200 mg)	I		H (03/02)	[3810-80-8]	$199

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1220302	22030-2	Dipivefrin Hydrochloride (200 mg)	I		H (06/99)	[64019-93-8]	$150
1220506	22050-6	Dipyridamole (200 mg)	H		G-1 (01/99)	[58-32-2]	$150
1220700	22070-0	Dirithromycin (200 mg)	F			[62013-04-1]	$150
1221000	22100-0	Disodium Guanylate (300 mg) (FCC)	F-1			[5550-12-9]	$150
1222002	22200-2	Disodium Inosinate (500 mg) (FCC)	F			[4691-65-0]	$150
1222501	22250-1	Disopyramide Phosphate (200 mg)	H-1		H (03/02)	[22059-60-5]	$150
1223005	22300-5	2,4-Disulfamyl-5-trifluoromethylaniline (125 mg)	G			[654-62-6]	$468
1224008	22400-8	Disulfiram (200 mg)	F-3		F-2 (07/02)	[97-77-8]	$150
1224507	22450-7	Dobutamine Hydrochloride (600 mg)	H-1		H (01/00)	[49745-95-1]	$150
1224700	22470-0	Docusate Calcium (500 mg)	H0B044		G-1 (07/02)	[128-49-4]	$150
1224802	22480-2	Docusate Sodium (500 mg)	J		I-1 (05/02)	[577-11-7]	$150
1224904	22490-4	Docusate Potassium (100 mg)	F-1		F (11/99)	[7491-09-0]	$150
1225204	22520-4	Dopamine Hydrochloride (200 mg)	G		F-5 (05/02)	[62-31-7]	$150
1225281		Dorzolamide Hydrochloride (500 mg)	F0C040			[130693-82-2]	$150
1225292		Dorzolamide Hydrochloride Related Compound A (20 mg) ((4R,6R)-4-(ethylamino)-5,6-dihydro-6-methyl-4H-thieno[2,3-b]thiopyran-2-sulfonamide 7,7-dioxide, monohydrochloride)	F0C068	1		n/f	$468
1225000	22500-0	Doxapram Hydrochloride (200 mg)	F-3			[7081-53-0]	$150
1225500	22550-0	Doxepin Hydrochloride (500 mg)	I			[1229-29-4]	$150
1225703	22570-3	Doxorubicin Hydrochloride (50 mg)	K		J (06/02)	[25316-40-9]	$461
1226003	22600-3	Doxycycline Hyclate (200 mg)	I		H (01/00)	[24390-14-5]	$150
1227006	22700-6	Doxylamine Succinate (300 mg)			H (01/04)	[562-10-7]	$150
1229001	22900-1	Droperidol (250 mg)	H-1		H (04/99)	[548-73-2]	$150
1230000	23000-0	Dyclonine Hydrochloride (200 mg)	G			[536-43-6]	$150
1231003	23100-3	Dydrogesterone (200 mg)	I0B114		H (01/04)	[152-62-5]	$150
1231502	23150-2	Dyphylline (200 mg)	G-2		G-1 (11/02)	[479-18-5]	$150
1231808	23180-8	Econazole Nitrate (200 mg)	G			[68797-31-9]	$150
1232006	23200-6	Edetate Calcium Disodium (200 mg)	G-3		G-2 (11/99)	[23411-34-9]	$150
1233009	23300-9	Edetate Disodium (200 mg)	H		G-2 (04/02)	[6381-92-6]	$150
1233508	23350-8	Edetic Acid (200 mg)	F-1			[60-00-4]	$150
1234001	23400-1	Edrophonium Chloride (200 mg)	H		G (08/99)	[116-38-1]	$150
1234806		Emedastine Difumarate (100 mg)	F0C059			[87233-62-3]	$150
1235004	23500-4	Emetine Hydrochloride (300 mg)	H0B201		G (05/03)	[316-42-7]	$150
1235274	23527-4	Enalaprilat (300 mg)	I		H (03/01) G (08/99)	[84680-54-6]	$119
1235300	23530-0	Enalapril Maleate (200 mg)	J		I (06/01)	[76095-16-4]	$150
1235503	23550-3	Endotoxin (10,000 USP Endotoxin Units)	G2B274		G-1 (12/03) G (06/99)	n/f	$150
1235809	23580-9	Enflurane (1 mL)	G-1		G (02/01)	[13838-16-9]	$150
1236007	23600-7	Ephedrine Sulfate (200 mg) **(List Chemical)**	H-2		H-1 (11/02)	[134-72-5]	$150
1236506	23650-6	4-Epianhydrotetracycline Hydrochloride (50 mg)	J0C041		I-1 (12/03) I (06/00)	[4465-65-0]	$468
1236801	23680-1	Epilactose (200 mg)	G		F-1 (06/00)	[103302-12-1]	$468
1237000	23700-0	Epinephrine Bitartrate (200 mg)	O			[51-42-3]	$150
1237509	23750-9	Epitetracycline Hydrochloride (200 mg)	F			[23313-80-6]	$468
1238002	23800-2	Equilin (25 mg)	I		H-1 (05/00)	[474-86-2]	$200
1239005	23900-5	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275		O (02/04) N (12/99)	[50-14-6]	$162
1239504	23950-4	Ergoloid Mesylates (300 mg)	I		H-1 (01/00)	[8067-24-1]	$150

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1240004	24000-4	Ergonovine Maleate (100 mg) **(List Chemical)**	N		M-1 (07/02)	[129-51-1]	$150
1241007	24100-7	Ergosterol (50 mg)	H			[57-87-4]	$150
1241506	24150-6	Ergotamine Tartrate (150 mg) **(List Chemical)**	I0B174		H (01/04)	[379-79-3]	$150
1241550	24155-0	Ergotaminine (100 mg) **(List Chemical)**	F-1			[639-81-6]	$150
1242000	24200-0	Erythromycin (250 mg)	M		L (08/99)	[114-07-8]	$150
1242010	24201-0	Erythromycin B (150 mg)	G		F-1 (09/01) F (05/01)	[527-75-3]	$150
1242021	24202-1	Erythromycin C (50 mg)	F-3		F-2 (01/03) F-1 (02/02) F (02/99)	n/f	$150
1242032	24203-2	Erythromycin Related Compound N (50 mg) (N-Demethylerythromycin A)	F-1		F (09/99)	n/f	$150
1243002	24300-2	Erythromycin Estolate (200 mg)	H		G (01/03)	[3521-62-8]	$150
1245008	24500-8	Erythromycin Ethylsuccinate (200 mg)	H		G-1 (06/01)	[1264-62-6]	$150
1246000	24600-0	Erythromycin Gluceptate (200 mg)	H		G (07/03)	[23067-13-2]	$150
1247003	24700-3	Erythromycin Lactobionate (200 mg)	H-1		H (01/02)	[3847-29-8]	$150
1248006	24800-6	Erythromycin Stearate (200 mg)	H0B187		G-1 (05/03)	[643-22-1]	$150
1249009	24900-9	Erythrosine Sodium (100 mg)	F			[49746-10-3]	$150
1250008	25000-8	Estradiol (500 mg)	K1B007		K (04/03)	[50-28-2]	$150
1251000	25100-0	Estradiol Benzoate (250 mg) (AS)	G-1			[50-50-0]	$150
1252003	25200-3	Estradiol Cypionate (200 mg)	G-1		G (02/00)	[313-06-4]	$150
1254009	25400-9	Estradiol Valerate (100 mg)	L		K (05/02)	[979-32-8]	$150
1254508	25450-8	Estriol (100 mg)	J		I-1 (06/01)	[50-27-1]	$150
1255001	25500-1	Estrone (200 mg)	K1B099		K (07/03) J-1 (07/00)	[53-16-7]	$150
1255500	25550-0	Estropipate (500 mg)	J0B262		I (12/03) H (09/01)	[7280-37-7]	$150
1256004	25600-4	Ethacrynic Acid (200 mg)	F			[58-54-8]	$150
1257007	25700-7	Ethambutol Hydrochloride (200 mg)	H		G (08/02)	[1070-11-7]	$150
1258305	25830-5	Ethchlorvynol **CIV** (0.7 ml)	F0B011			[113-18-8]	$199
1260001	26000-1	Ethinyl Estradiol (150 mg)	P1B193		P0B052 (01/04) P (03/03) O (08/99)	[57-63-6]	$150
1260012		Ethinyl Estradiol Related Compound A (20 mg) (6-Keto-ethinyl estradiol)	F0B252			n/f	$468
1261004	26100-4	Ethionamide (200 mg)	H0B148		G (03/03)	[536-33-4]	$150
1262801	26280-1	Ethopabate (125 mg)	F			[59-06-3]	$150
1262823	26282-3	Ethopabate Related Compound A (25 mg) (Methyl-4-acetamido-2-hydroxybenzoate)	F			n/f	$468
1263000	26300-0	Ethopropazine Hydrochloride (300 mg)	G			[1094-08-2]	$150
1264002	26400-2	Ethosuximide (125 mg)	H		G-2 (11/01) G-1 (05/99)	[77-67-8]	$119
1264501	26450-1	Ethotoin (200 mg)	F			[86-35-1]	$150
1265005	26500-5	Ethoxzolamide (200 mg)	F			[452-35-7]	$150
1265504	26550-4	Ethylcellulose (1 g)	H-1		H (06/99)	[9004-57-3]	$150
1266008	26600-8	Ethyl Maltol (1 g) (FCC)	H			[4940-11-8]	$150
1266507	26650-7	Ethylnorepinephrine Hydrochloride (200 mg)	F			[3198-07-0]	$150
1267000	26700-0	Ethylparaben (200 mg)	I0A016		H (01/04)	[120-47-8]	$150
1267500	26750-0	Ethyl Vanillin (200 mg)	F2B134	2	F-1 (04/04)	[121-32-4]	$150
1268003	26800-3	Ethynodiol Diacetate (200 mg)	I0A033		H-1 (01/03) H (04/01)	[297-76-7]	$150

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1268502	26850-2	Etidronate Disodium (200 mg)	G		F-2 (02/03)	[7414-83-7]	$150
1268604	26860-4	Etidronic Acid Monohydrate (1 g)	G		F-1 (05/99)	[2809-21-4]	$150
1268706	26870-6	Etodolac (400 mg)	G		F (10/01)	[41340-25-4]	$150
1268728	26872-8	Etodolac Related Compound A (25 mg) ((˘)-8-ethyl-l-methyl-1,3,4,9-tetrahydropyrano [3,4-beta]-indole-1-acetic acid)	F-1		F (05/02)	[109518-50-5]	$200
1268808	26880-8	Etoposide (300 mg)	G			[33419-42-0]	$119
1268852		Etoposide Resolution Mixture (30 mg)	F0B209			[33419-42-0]	$200
1269006	26900-6	Evans Blue (200 mg)			G (04/04)	[314-13-6]	$150
1269200	26920-0	Famotidine (125 mg)	H-1		H (11/02) G (03/99)	[76824-35-6]	$119
1269389	26938-9	Felodipine (200 mg)	F-1		F (09/02)	[72509-76-3]	$150
1269390		Felodipine Related Compound A (100 mg) (ethyl methyl 4-(2,3-dichlorophenyl)-2,6-dimethylpyridine-3,5-dicarboxylate)	F0B207			[96302-71-7]	$468
1269403	26940-3	Fenbendazole (100 mg)	F			[43210-67-9]	$468
1269458		Fenoldopam Mesylate (200 mg)	F0C125	1		[67227-57-0]	$150
1269469		Fenoldopam Related Compound A (20 mg) (1-Methyl-3-benzazapine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate)	F0C124	1		n/f	$468
1269470		Fenoldopam Related Compound B (20 mg) (1H-3-Benzazapine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate)	F0C126	1		n/f	$468
1269505	26950-5	Fenoprofen Calcium (500 mg)	G-1			[53746-45-5]	$150
1269550	26955-0	Fenoprofen Sodium (500 mg)	G		F-1 (05/02)	[66424-46-2]	$150
1270005	27000-5	Fentanyl Citrate **CII** (100 mg)	J2B227		J-1 (09/03) J (05/02) I (06/00)	[990-73-8]	$199
1270402	27040-2	Finasteride (200 mg)	F			[98319-26-7]	$150
1270800	27080-0	Flecainide Acetate (200 mg)	F-1		F (06/03)	[54143-56-5]	$150
1270821	27082-1	Flecainide Related Compound A (75 mg) (3-[2,5-bis(2,2,2-trifluoroethoxy)phenyl]-1,5,6,7,8,8a-hexahydroimidazo-[1,5a]pyridine Hydrochloride)	F			n/f	$468
1271008	27100-8	Floxuridine (250 mg)	F-2		F-1 (08/01)	[50-91-9]	$150
1272000	27200-0	Flucytosine (200 mg)	F			[2022-85-7]	$150
1273003	27300-3	Fludrocortisone Acetate (250 mg)	H		G (08/01)	[514-36-3]	$150
1274006	27400-6	Flumethasone Pivalate (200 mg)	I		H (01/02)	[2002-29-1]	$150
1274505	27450-5	Flunisolide (200 mg)	I		H (01/01)	[77326-96-6]	$150
1274607	27460-7	Flunixin Meglumine (300 mg)	G		F-1 (04/02) F (09/99)	[42461-84-7]	$150
1275009	27500-9	Fluocinolone Acetonide (100 mg)	J		I (11/99)	[67-73-2]	$150
1276001	27600-1	Fluocinonide (100 mg)	I			[356-12-7]	$150
1277004	27700-4	Fluorescein (200 mg)	G0B171		F-1 (02/03)	[2321-07-5]	$150
1277208	27720-8	Fluoride Dentifrice: Sodium Fluoride-Calcium Pyrophosphate (high beta-phase) (180 g)			F (01/04)	n/f	$468
1277252	27725-2	Fluoride Dentifrice: Sodium Fluoride/Silica (4.5 oz)	I		H (04/99)	n/f	$440
1277274	27727-4	Fluoride Dentifrice: Sodium Fluoride/Sodium Bicarbonate Powder (4 oz)	F			n/f	$468
1277300	27730-0	Fluoride Dentifrice: Sodium Monofluorophosphate-Calcium Carbonate (4.6 oz)	G			n/f	$468
1277354	27735-4	Fluoride Dentifrice: Sodium Monofluorophosphate/Dicalcium Phosphate (4.6 oz)	G			n/f	$468

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1277401	27740-1	Fluoride Dentifrice: Sodium Monofluorophosphate (1000 ppm)/Silica (5.25 oz)	G-1		G (08/99)	n/f	$468
1277423	27742-3	Fluoride Dentifrice: Sodium Monofluorophosphate (1500 ppm)/Silica (5.25 oz)	F-1		F (07/99)	n/f	$468
1277456	27745-6	Fluoride Dentifrice: Stannous Fluoride-Silica (4 oz)	H0B105		G (11/02)	n/f	$468
1278007	27800-7	Fluorometholone (200 mg)	I0B184		H-1 (11/02)	[426-13-1]	$150
1278109	27810-9	Fluorometholone Acetate (200 mg)	F			[3801-06-7]	$150
1278302	27830-2	Fluoroquinolonic Acid (50 mg)	G		F-1 (12/99)	[86393-33-1]	$468
1279000	27900-0	Fluorouracil (250 mg)	H-1		H (01/02)	[51-21-8]	$150
1279804	27980-4	Fluoxetine Hydrochloride (200 mg)	F-1		F (11/99)	[59333-67-4]	$150
1279815	27981-5	Fluoxetine Related Compound A (15 mg) (N-methyl-3-phenyl-3-[(alpha,alpha,alpha-(trifluoro-m-tolyl)oxy]propylamine Hydrochloride)	G		F-1 (05/01) F (06/00)	n/f	$468
1279826	27982-6	Fluoxetine Related Compound B (5 mL of a 0.01N HCl solution, approx. 2 mg/mL) (N-methyl-3-phenylpropylamine)	F-2		F-1 (09/02) F (09/00)	[23580-89-4]	$150
1280009	28000-9	Fluoxymesterone **CIII** (200 mg)	G-2		G-1 (04/00)	[76-43-7]	$199
1280803	28080-3	Fluphenazine Decanoate Dihydrochloride (500 mg)	G		F-1 (10/01)	n/f	$153
1281001	28100-1	Fluphenazine Enanthate Dihydrochloride (125 mg)	H		G (02/99)	[3105-68-8]	$119
1282004	28200-4	Fluphenazine Hydrochloride (125 mg)	H			[146-56-5]	$119
1284000	28400-0	Flurandrenolide (100 mg)	I0B245		H (09/03)	[1524-88-5]	$150
1285002	28500-2	Flurazepam Hydrochloride **CIV** (200 mg)	I			[1172-18-5]	$199
1285308	28530-8	Flurazepam Related Compound C (50 mg) (5-chloro-2-(2-diethylaminoethyl(amino)-2'-fluorobenzophenone Hydrochloride)	H-1			n/f	$468
1285603	28560-3	Flurazepam Related Compound F (50 mg) (7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-one)	I0C092	2	H (01/04)	[2886-65-9]	$468
1285750	28575-0	Flurbiprofen (200 mg)	G			[5104-49-4]	$150
1285760	28576-0	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)	H		G (03/01)	n/f	$468
1285807	28580-7	Flurbiprofen Sodium (200 mg)	F			[56767-76-1]	$150
1285851	28585-1	Flutamide (200 mg)	G		F-1 (06/00)	[13311-84-7]	$150
1285862	28586-2	o-Flutamide (50 mg)	F-1		F (01/00)	n/f	$150
1286005	28600-5	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P		O (07/00)	[59-30-3]	$150
1286027	28602-7	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176	2	H-1 (04/04) H (01/00)	[1492-18-8]	$150
1286209	28620-9	4-Formylbenzenesulfonamide (50 mg)	F			n/f	$468
1286300	28630-0	10-Formylfolic Acid (25 mg)	F2B226		F-1 (01/4)	[134-05-4]	$150
1286366		Fosphenytoin Sodium (250 mg)	F0C156	1		[92134-98-0]	$150
1286504	28650-4	Fructose (125 mg)	I-2		I-1 (11/02) I (08/99)	[57-48-7]	$119
1286708	28670-8	Fumaric Acid (200 mg)	G-1		G (04/02)	[110-17-8]	$150
1286800	28680-0	Furazolidone (200 mg)	G-2		G-1 (01/01)	[67-45-8]	$150
1287008	28700-8	Furosemide (125 mg)	J1B131		J (10/03)	[54-31-9]	$119
1287020	28702-0	Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid)	J		I (08/02)	n/f	$468
1287030	28703-0	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)	H		G-3 (03/01)	[3086-91-7]	$468
1287303	28730-3	Gabapentin (250 mg)	F			[60142-96-3]	$150
1287325	28732-5	Gabapentin Related Compound A (100 mg) (3,3-pentamethylene-5-butyrolactam)	F			[64744-50-9]	$468
1287507	28750-7	Gadodiamide (500 mg)	F			[131410-48-5]	$150

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1287518	28751-8	Gadodiamide Related Compound A (50 mg) (gadolinium sodium diethylenetriamine pentaacetic acid monomethylamide)	F			n/f	$468
1287529	28752-9	Gadodiamide Related Compound B (50 mg) (gadolinium disodium diethylenetriamine pentaacetic acid)	F			[131410-48-5]	$468
1287609	28760-9	Gadopentetate Monomeglumine (500 mg)	F			[92923-57-4]	$150
1287631	28763-1	Gadoteridol (500 mg)	F			[120066-54-8]	$150
1287642	28764-2	Gadoteridol Related Compound A (50 mg) (10-(2-hydroxypropyl)-1,4,7,10-tetraazacyclododecane-1,4,7-triaacetic acid)	F0A002			[120041-08-9]	$468
1287653		Gadoteridol Related Compound B (50 mg) (1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, monogadolinium salt)	F0B198			[112188-16-6]	$468
1287664		Gadoteridol Related Compound C (50 mg) (1,4,7,10-Tetraaza-11-oxo-bicyclo[8.2.2]tetradecane-4,7-diacetic acid)	F0B199			[220182-19-4]	$468
1287700	28770-0	Galactose (200 mg)	F-4		F-3 (05/01)	[59-23-4]	$468
1288000	28800-0	Gallamine Triethiodide (200 mg)	F			[65-29-2]	$150
1288500	28850-0	Gemfibrozil (200 mg)	H			[25812-30-0]	$150
1288510		Gemfibrozil Related Compound A (20 mg) (2,2-dimethyl-5-[2,5-dimethyl-4-propene-1-yl)phenoxy]valeric acid)	F0C101	1		n/f	$468
1289003	28900-3	Gentamicin Sulfate (200 mg)	K		J-1 (04/00)	[1405-41-0]	$150
1290002	29000-2	Gentian Violet (650 mg)	F			[548-62-9]	$150
1291005	29100-5	Gibberellic Acid (200 mg) (FCC)	G		F (04/01)	[77-06-5]	$150
1291504	29150-4	Powdered Ginger (500 mg)	F			n/f	$150
1291708		Powdered Asian Ginseng Extract (1.5 g)	F0B289			[50647-08-0]	$500
1292008	29200-8	Gitoxin (50 mg)	G		F-3 (07/00)	[4562-36-1]	$468
1292507	29250-7	Glipizide (125 mg)	G			[29094-61-9]	$119
1292609	29260-9	Glipizide Related Compound A (25 mg) (N-{2-[(4-aminosulfonyl)phenyl]ethyl}-5-methyl-pyrazinecarboxamide)	G-1		G (04/99)	n/f	$468
1294003	29400-3	Glucagon (25 mg, 0.95 U/mg)	H			[16941-32-5]	$150
1294976		Glutamic Acid (200 mg)	F0C069			[56-86-0]	$150
1294808		Glutamine (100 mg)	F0B244			[56-85-9]	$150
1294848	29484-8	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F			n/f	$649
1295006	29500-6	Glutethimide **CII** (500 mg)	F			[77-21-4]	$199
1295505	29550-5	Glyburide (200 mg)	G		F-2 (11/02)	[10238-21-8]	$150
1295607	29560-7	Glycerin (2 mL)	H0C073	2	G1A001 (04/04) G (12/02) F (04/99)	[56-81-5]	$150
1295709	29570-9	Glyceryl Behenate (200 mg)	F3B113		F-2 (03/03)	[18641-57-1]	$150
1295800	29580-0	Glycine (200 mg)	F-3		F-2 (02/00)	[56-40-6]	$150
1296009	29600-9	Glycopyrrolate (200 mg)	H0B304	2	G (05/04)	[596-51-0]	$150
1295888		Glycyrrhizic Acid (25 mg)	F0C006	1		[1405-86-3]	$468
1297001	29700-1	Human Chorionic Gonadotropin (1 vial, 5,760 USP Units per package)	H		G (07/00)	[9002-61-3]	$150
1298004	29800-4	Gramicidin (200 mg)	I		H-1 (07/02)	[1405-97-6]	$150
1299007	29900-7	Griseofulvin (200 mg)	I		H-1 (09/02)	[126-07-8]	$150
1299200	29920-0	Griseofulvin Permeability Diameter (2 g)	I0C138	2	H (08/03)	[126-07-8]	$150
1300004	30000-4	Guaiacol (1 g)	K		J (04/00)	[90-05-1]	$150
1301007	30100-7	Guaifenesin (200 mg)	I		H (09/02)	[93-14-1]	$150
1301404	30140-4	Guanabenz Acetate (200 mg)	G		F-1 (06/00)	[23256-50-0]	$150
1301608	30160-8	Guanadrel Sulfate (200 mg)	F-1			[22195-34-2]	$150
1301801	30180-1	Guanethidine Monosulfate (200 mg)	F			[645-43-2]	$150

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1302000	30200-0	Guanethidine Sulfate (500 mg)	G-1			[60-02-6]	$150
1302101	30210-1	Guanfacine Hydrochloride (125 mg)	G0B123		F-1 (02/03) F (11/99)	[29110-48-3]	$119
1302305	30230-5	Halazepam **CIV** (200 mg)	F			[23092-17-3]	$199
1302509	30250-9	Halcinonide (300 mg)	F			[3093-35-4]	$150
1303002	30300-2	Haloperidol (200 mg)	I		H-1 (05/02)	[52-86-8]	$150
1303013	30301-3	Haloperidol Related Compound A (25 mg) (4,4-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone)	J			[67987-08-0]	$468
1303308	30330-8	Haloprogin (200 mg)	F			[777-11-7]	$150
1303501	30350-1	Halothane (1 mL)	F-1			[151-67-7]	$150
1304005	30400-5	Heparin Sodium (10 x 1 mL)	K-5		K-4 (08/03) K-3 (02/99)	[9041-08-1]	$150
1305008	30500-8	Hexachlorophene (500 mg)	I		H-2 (01/01)	[70-30-4]	$150
1307003	30700-3	Hexobarbital **CIII** (500 mg)	F			[56-29-1]	$199
1308006	30800-6	Hexylcaine Hydrochloride (1 g)	F-1			[532-76-3]	$150
1308200	30820-0	Hexylene Glycol (125 mg)	G		F-2 (04/02) F-1 (04/99)	[107-41-5]	$150
1308307	30830-7	Hexylresorcinol (200 mg)	F			[136-77-6]	$150
1308505	30850-5	L-Histidine (200 mg)	G0A018		F-2 (01/03) F-1 (04/00)	[71-00-1]	$150
1309009	30900-9	Histamine Dihydrochloride (250 mg)	L			[56-92-8]	$150
1310008	31000-8	Homatropine Hydrobromide (200 mg)	H-1		H (08/02)	[51-56-9]	$150
1311000	31100-0	Homatropine Methylbromide (250 mg)	J		I-1 (06/01) H-1 (10/01)	[80-49-9]	$150
1311408	31140-8	Homosalate (500 mg/ampule)	F0B102			[118-56-9]	$150
1312003	31200-3	Hyaluronidase (500 mg)	H			[9001-54-1]	$150
1313006	31300-6	Hydralazine Hydrochloride (200 mg)	K		J-1 (09/02)	[304-20-1]	$150
1314009	31400-9	Hydrochlorothiazide (200 mg)	I		H (05/02)	[58-93-5]	$150
1315001	31500-1	Hydrocodone Bitartrate **CII** (250 mg)	J0A026		I-1 (12/02) I (07/02) H-2 (11/99)	[34195-34-1]	$199
1316004	31600-4	Hydrocortisone (200 mg)	M		L (09/00)	[50-23-7]	$150
1317007	31700-7	Hydrocortisone Acetate (200 mg)	K		J (10/99)	[50-03-3]	$150
1317302	31730-2	Hydrocortisone Butyrate (200 mg)	H			[13609-67-1]	$150
1318000	31800-0	Hydrocortisone Cypionate (200 mg)	F			[508-99-6]	$150
1319002	31900-2	Hydrocortisone Hemisuccinate (200 mg)	H		G-3 (03/02) G-2 (08/99)	[83784-20-7]	$150
1320001	32000-1	Hydrocortisone Phosphate Triethylamine (200 mg)	F-1			n/f	$150
1321004	32100-4	Hydrocortisone Valerate (200 mg)	F-1		F (07/02)	[57524-89-7]	$150
1322007	32200-7	Hydroflumethiazide (200 mg)	F-2			[135-09-1]	$150
1323000	32300-0	Hydromorphone Hydrochloride **CII** (50 mg)	I		H-2 (03/01)	[71-68-1]	$199
1324002	32400-2	Hydroquinone (500 mg)	G-1		G (11/01) F-4 (02/99)	[123-31-9]	$150
1325005	32500-5	Hydroxyamphetamine Hydrobromide (200 mg)	G		F (06/01)	[306-21-8]	$150
1327000	32700-0	Hydroxychloroquine Sulfate (200 mg)	I			[747-36-4]	$150
1329006	32900-6	Hydroxyprogesterone Caproate (200 mg)	H			[630-56-8]	$150
1329709		Hydroxypropyl Betadex (200 mg)	F0B295			[128446-35-5]	$150
1329800	32980-0	Hydroxypropyl Cellulose (200 mg)	F-1			[9004-64-2]	$150
1330005	33000-5	Hydroxypropyl Methylcellulose (250 mg)	G-1		G (02/02)	[9004-65-3]	$150
1332000	33200-0	Hydroxyurea (200 mg)	H		G (01/00)	[127-07-1]	$150
1333003	33300-3	Hydroxyzine Hydrochloride (500 mg)	H			[2192-20-3]	$150

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1333058	33305-8	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)	H			[303-26-4]	$200
1334006	33400-6	Hydroxyzine Pamoate (500 mg)	H0C016		G-1 (07/03)	[10246-75-0]	$150
1335009	33500-9	Hyoscyamine Sulfate (125 mg)	G2A007		G-1 (08/02) G (10/99)	[6835-16-1]	$119
1335202	33520-2	Hyperoside (50 mg)	F			[482-36-0]	$822
1335304	33530-4	Hypromellose Phthalate (100 mg)	F-1		F (12/00)	[9050-31-1]	$150
1335508	33550-8	Ibuprofen (750 mg)	J		I (06/02)	[15687-27-1]	$150
1335701	33570-1	Idarubicin Hydrochloride (50 mg)	H0C061		G (11/03) F (06/00)	[57852-57-0]	$461
1336001	33600-1	Idoxuridine (250 mg)	H			[54-42-2]	$150
1336205	33620-5	Ifosfamide (500 mg)	G		F-1 (11/00) F (02/99)	[3778-73-2]	$150
1336500	33650-0	Imidazole (200 mg)	G1B132		G (01/04)	[288-32-4]	$468
1336806	33680-6	Imidurea (200 mg)	H		G (10/99)	[39236-46-9]	$150
1337004	33700-4	Iminodibenzyl (25 mg)	H			[494-19-9]	$468
1337809	33780-9	Imipenem Monohydrate (100 mg)	G		F (01/01)	[74431-23-5]	$150
1338007	33800-7	Imipramine Hydrochloride (200 mg)	I		H (09/01)	[113-52-0]	$150
1338801	33880-1	Indapamide (250 mg)	H		G (07/02)	[26807-65-8]	$150
1339000	33900-0	Indigotindisulfonate Sodium (500 mg)	H1B153		H (06/03)	[860-22-0]	$150
1340009	34000-9	Indocyanine Green (200 mg)	I0B045		H (09/01)	[3599-32-4]	$150
1341001	34100-1	Indomethacin (200 mg)	J0B165		I (01/04) H (05/99)	[53-86-1]	$150
1342004	34200-4	Insulin (100 mg)	H			[9004-10-8]	$150
1342106	34210-6	Insulin Human (100 mg)	H1A031		H (11/02) G (04/00)	[11061-68-0]	$150
1342208	34220-8	Insulin (Beef) (100 mg)	F			[11070-73-8]	$150
1342300	34230-0	Insulin (Pork) (100 mg)	F			[12584-58-6]	$150
1342503	34250-3	Iocetamic Acid (200 mg)	F			[16034-77-8]	$150
1343007	34300-7	Iodipamide (200 mg)	G			[606-17-7]	$150
1343517		Iodixanol (200 mg)	F0B240			[92339-11-2]	$150
1343540		Iodixanol Related Compound C (25 mg) (5-Acetyl[3-[[3,5-bis[[2,3-dihydroxypropyl)amino]carbonyl]-2,4,6-triiodophenyl]amino]-2-hydroxypropyl]amino]-N,N'-bis-(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B236			n/f	$468
1343550		Iodixanol Related Compound D (50 mg) (5-[Acetyl(2-hydroxy-3-methylpropyl)amino]-N,N'-bis(2,3-dihydroxypropyl)2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B231			[89797-00-2]	$468
1343561		Iodixanol Related Compound E (25 mg) (5-[[3-[[3-[[(2,3-Dihydoxypropyl)amino]carbonyl]-5-[[amino]carbonyl]-2,4,6-triiodophenyl](acetylimino)]-2-hydroxypropyl]-(acetylimino)]-N,N'-bis(2,3-dihydoxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F0B229			n/f	$468
1344305	34430-5	o-Iodohippuric Acid (100 mg)	F			[147-58-0]	$150
1344509	34450-9	Iodoquinol (100 mg)	H		G (07/02)	[83-73-8]	$150
1344600	34460-0	Iohexol (100 mg)	F-1		F (01/99)	[66108-95-0]	$119
1344622	34462-2	Iohexol Related Compound A (100 mg) (5-(acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F-1		F (10/01)	n/f	$468
1344644	34464-4	Iohexol Related Compound B (50 mg) (5-amino-*N,N'*-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-1,3-benzenedicarboxamide)	F-1		F (01/04)	[76801-93-9]	$468

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1344666	34466-6	Iohexol Related Compound C (100 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-nitro-1,3-benzenedicarboxamide)	F-1		F (09/03)	n/f	$150
1344702	34470-2	Iopamidol (200 mg)	G			[60166-93-0]	$150
1344724	34472-4	Iopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoiso-phthalamide)	G			[60166-98-5]	$468
1344735	34473-5	Iopamidol Related Compound B (100 mg) (5-Glycolamido-N,N'-bis[2-hydroxy-1-(hydroxymethyl)ethyl]-2,4,6-triiodoisophthalamide)	F			n/f	$468
1344804	34480-4	Iopromide (400 mg)	F			[73334-07-3]	$150
1344826	34482-6	Iopromide Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide)	F			n/f	$468
1344837	34483-7	Iopromide Related Compound B (50 mg) (5-(Acetylamino)-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodo-N-methyl-1,3-benzenedicarboxamide)	F			n/f	$468
1345002	34500-2	Iothalamic Acid (200 mg)	G			[2276-90-6]	$150
1345104	34510-4	Ioversol (200 mg)	F			[87771-40-2]	$150
1345115	34511-5	Ioversol Related Compound A (50 mg) (5-Amino-N,N'-bis(2,3-dihydroxypropyl)-2,4,6-triiodoisophthalamide)	F			[76801-93-9]	$468
1345126	34512-6	Ioversol Related Compound B (50 mg) (N,N'-bis(2,3-dihydroxypropyl)-5-[(N-(2-hydroxyethyl)-carbonyl)methoxy]-2,4,6-triiodoisophthalamide)	F			n/f	$468
1345159	34515-9	Ioxaglic Acid (100 mg)	F			[59017-64-0]	$150
1345206	34520-6	Ioxilan (400 mg)	F			[107793-72-6]	$150
1345228	34522-8	Ioxilan Related Compound A (100 mg) (5-amino-2,4,6-triiodo-3 N-(2-hydroxyethyl)carbamoyl benzoic acid)	F			[22871-58-5]	$468
1346005	34600-5	Ipodate Calcium (200 mg)	F			[1151-11-7]	$150
1347008	34700-8	Ipodate Sodium (200 mg)	F-1			[1221-56-3]	$150
1347755	34775-5	Isoamyl Methoxycinnamate (750 mg/ampule)	F0B017			[71617-10-2]	$150
1348000	34800-0	Isocarboxazid (200 mg)	F-1			[59-63-2]	$150
1348500	34850-0	Isoetharine Hydrochloride (250 mg)	F-2			[2576-92-3]	$150
1348907		Isoflupredone Acetate (200 mg)	F0C109	1		[338-98-7]	$150
1349003	34900-3	Isoflurane (1 mL)	H			[26675-46-7]	$150
1349502	34950-2	L-Isoleucine (200 mg)	F-2		F-1 (09/02)	[73-32-5]	$150
1349604	34960-4	Isomalathion (50 mg)	F1B107		F (01/03)	[3344-12-5]	$468
1349659	34965-9	Isometheptene Mucate (200 mg)	F			[7492-31-1]	$150
1349706	34970-6	Isoniazid (200 mg)	H			[54-85-3]	$150
1350002	35000-2	Isopropamide Iodide (200 mg)	F-2			[71-81-8]	$150
1350400	35040-0	Isopropyl Myristate (500 mg)	I			[110-27-0]	$150
1350603	35060-3	Isopropyl Palmitate (500 mg)	I		H (10/99)	[142-91-6]	$150
1351005	35100-5	Isoproterenol Hydrochloride (125 mg)	K			[51-30-9]	$119
1352008	35200-8	Isosorbide (75% solution, 1 g)	I		H-2 (10/00)	[652-67-5]	$150
1353000	35300-0	Diluted Isosorbide Dinitrate (500 mg of 25% mixture with mannitol)	I-1		I (10/99)	[87-33-2]	$150
1353500	35350-0	Isotretinoin (200 mg)	I		H (10/00)	[4759-48-2]	$150
1354003	35400-3	Isoxsuprine Hydrochloride (200 mg)	F-3			[579-56-6]	$150
1354207	35420-7	Isradipine (200 mg)	G0B054		F (05/03)	[75695-93-1]	$150
1354218	35421-8	Isradipine Related Compound A (25 mg) (Isopropyl methyl 4-(4-benzofurazanyl)-2,6-dimethyl-3,5-pyridinecarboxylate)	F			n/f	$468
1354309		Ivermectin (200 mg)	F0B196			[70288-86-7]	$150
1355006	35500-6	Kanamycin Sulfate (200 mg)	J		I (06/99)	[25389-94-0]	$150

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1356009	35600-9	Ketamine Hydrochloride **CIII** (250 mg)	G-2		G-1 (07/00)	[1867-66-9]	$199
1356020		Ketamine Related Compound A (50 mg) (1-[(2-Chlorophenyl)(methylimino)methyl]cylcopentanol)	F0C118	1		[6740-87-0]	$468
1356508	35650-8	Ketoconazole (200 mg)	G4B179		G-3 (01/04) G-2 (06/01) G-1 (01/99)	[65277-42-1]	$150
1356632	35663-2	Ketoprofen (200 mg)	G		F-2 (05/99)	[22071-15-4]	$150
1356643	35664-3	Ketoprofen Related Compound A (25 mg) (alpha-Methyl-3-(4-methylbenzoyl) benzeneacetic acid)	G			[107257-20-5]	$468
1356665	35666-5	Ketorolac Tromethamine (200 mg)	G		F-2 (04/99)	[74103-07-4]	$150
1356654	35665-4	Labetalol Hydrochloride (200 mg)	G		F-2 (01/02) F-1 (03/01)	[32780-64-6]	$150
1356676	35667-6	Anhydrous Lactose (100 mg)	G		F (06/01)	[63-42-3]	$150
1356687	35668-7	Lactitol (500 mg)	F0B005			[81025-04-9]	$150
1356701	35670-1	Lactose Monohydrate (500 mg)	G-1		G (08/02)	[5989-81-1]	$150
1356803	35680-3	Lactulose (1 g)	H		G-1 (08/00)	[4618-18-2]	$150
1356880	35688-0	Lanolin (20 g)	F			[8006-54-0]	$150
1356905	35690-5	Lanolin Alcohols (5 g)	F			[8027-33-6]	$150
1356916		Lansoprazole (200 mg)	F0B310			[103577-45-3]	$150
1356927		Lansoprazole Related Compound A (25 mg) (2-[[[3-methyl-4-(2,2,2-triflouroethoxy)-2-pyridyl]methyl]sulfonyl]benzimidazole)	F0B311			n/f	$468
1356971		Letrozole (200 mg)	F0B170			[112809-51-5]	$150
1356982		Letrozole Related Compound A (15 mg) (4,4'-(1H-1,3,4-triazol-1-ylmethylene)dibenzonitrile)	F0B168			n/f	$468
1357001	35700-1	L-Leucine (200 mg)	H0B237	2	G-1 (04/04) G (08/00)	[61-90-5]	$150
1358004	35800-4	Leucovorin Calcium (500 mg)	J-1		J (05/02)	[1492-18-8]	$154
1359007	35900-7	Levallorphan Tartrate (200 mg)	G-1		G (11/02)	[71-82-9]	$150
1359302	35930-2	Levamisole Hydrochloride (125 mg)	F-1			[16595-80-5]	$119
1359506	35950-6	Levmetamfetamine **CII** (75 mg)	F			[33817-09-3]	$199
1359801	35980-1	Levobunolol Hydrochloride (200 mg)	G			[27912-14-7]	$150
1359903	35990-3	Levocarnitine (400 mg)	G0B197		F-2 (06/03) F-1 (12/00)	[541-15-1]	$150
1359925	35992-5	Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride)	F-1		F (08/01)	[6538-82-5]	$200
1361009	36100-9	Levodopa (200 mg)	I		H (09/00)	[59-92-7]	$150
1361010	36101-0	Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)-alanine)	K		J (01/03) I (06/00)	[27244-64-0]	$468
1362001	36200-1	Levo-alpha-acetylmethadol Hydrochloride **CII** (25 mg) (AS)			F-1 (08/03) F (07/01)	[43033-72-3]	$199
1362500	36250-0	Levonordefrin (200 mg)	F-1			[829-74-3]	$150
1363004	36300-4	Levopropoxyphene Napsylate (300 mg)	G			[55557-30-7]	$150
1364007	36400-7	Levorphanol Tartrate **CII** (500 mg)	H		G (03/01)	[5985-38-6]	$199
1365000	36500-0	Levothyroxine (500 mg)	K		J (10/00)	[51-48-9]	$150
1366002	36600-2	Lidocaine (250 mg)	L			[137-58-6]	$150
1367005	36700-5	Lincomycin Hydrochloride (200 mg)	H2B130		H-1 (01/04)	[7179-49-9]	$150
1367504	36750-4	Lindane (200 mg)	F-2			[58-89-9]	$150
1368008	36800-8	Liothyronine (250 mg)	L		K (08/01)	[6893-02-3]	$150
1368609	36860-9	Lisinopril (300 mg)	I		H (09/01) G (10/99)	[83915-83-7]	$150

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1369000	36900-0	Lithium Carbonate (300 mg)	G0B031		F-2 (01/03) F-1 (01/01)	[554-13-2]	$150
1370000	37000-0	Loperamide Hydrochloride (200 mg)	G-2		G-1 (02/03)	[34552-83-5]	$150
1370203	37020-3	Loracarbef (200 mg)	F			[121961-22-6]	$150
1370225	37022-5	Loracarbef L-Isomer (25 mg)	F			n/f	$150
1370305	37030-5	Lorazepam **CIV** (200 mg)	H0B023		G-2 (06/03)	[846-49-1]	$199
1370327	37032-7	Lorazepam Related Compound A (25 mg) (7-Chloro-5-(o-chlorophenyl)-1,3-dihydro-3-acetoxy-2H-1,4-benzodiazepin-2-one)	G		F-1 (06/01)	[2848-96-6]	$468
1370338	37033-8	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)	G		F-2 (01/04)	[2958-36-3]	$468
1370349	37034-9	Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde)	H		G (01/03) F-3 (01/02)	n/f	$468
1370350	37035-0	Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid)	G0A014		F-2 (01/04)	[54643-79-7]	$468
1370360	37036-0	Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol)	G		F-3 (07/02) F-2 (04/99)	n/f	$468
1370600	37060-0	Lovastatin (125 mg)	H2C012		H1B067 (01/04) H (08/03)	[75330-75-5]	$119
1370611		Lovastatin Related Compound A (20 mg) (Butanoic acid, 2-methyl-, 1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester, [1S-[alpha(R*), 3alpha,7beta,8beta(2S*,4S*), 8alpha beta]]-)	F0B235			n/f	$468
1370702	37070-2	Loxapine Succinate (125 mg)	G0B026		F-2 (06/03) F-1 (07/01) F (03/99)	[27833-64-3]	$119
1370906		Lynestrenol (20 mg)	F0B314			[52-76-6]	$195
1371002	37100-2	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) **(AS)** (LSD)	I			[50-37-3]	$199
1371501	37150-1	L-Lysine Acetate (200 mg)	F			[57282-49-2]	$150
1372005	37200-5	L-Lysine Hydrochloride (200 mg)	H		G (07/00)	[657-27-2]	$150
1373008	37300-8	Mafenide Acetate (200 mg)	F			[13009-99-9]	$150
1374000	37400-0	Magaldrate (200 mg)	F-1			[74978-16-8]	$150
1374306	37430-6	Magnesium Salicylate (200 mg)	F2B081	4	F-1 (01/04)	[18917-95-8]	$150
1374408	37440-8	Malathion (500 mg)	F-1		F (08/01)	[121-75-5]	$150
1374500	37450-0	Maleic Acid (300 mg)	G		F-2 (12/00)	[110-16-7]	$468
1374601	37460-1	Malic Acid (Racemic) (200 mg)	G0B158		F-1 (04/03)	[617-48-1]	$150
1374907	37490-7	Maltitol (200 mg)	G		F-1 (12/99)	[585-88-6]	$150
1375003	37500-3	Maltol (4 g) (FCC)	G		F-1 (12/99)	[118-71-8]	$150
1375058	37505-8	Mandelic Acid (500 mg)	F			[90-64-2]	$150
1375105	37510-5	Mannitol (200 mg)	I0B212	2	H (03/04)	[69-65-8]	$150
1375207	37520-7	Maprotiline Hydrochloride (200 mg)	H		G (07/02)	[10347-81-6]	$150
1375309	37530-9	Mazindol **CIV** (350 mg)	H		G (02/03)	[22232-71-9]	$199
1375502	37550-2	Mebendazole (200 mg)	G			[31431-39-7]	$150
1375706	37570-6	Mebrofenin (100 mg)	F			[78266-06-5]	$150
1376006	37600-6	Mecamylamine Hydrochloride (200 mg)	F-2			[826-39-1]	$150
1376505	37650-5	Mechlorethamine Hydrochloride (100 mg)	F-1		F (09/00)	[55-86-7]	$150
1377009	37700-9	Meclizine Hydrochloride (500 mg)	I-1			[31884-77-2]	$150
1377508	37750-8	Meclocycline Sulfosalicylate (300 mg)	G			[73816-42-9]	$150
1377803	37780-3	Meclofenamate Sodium (500 mg)	H			[6385-02-0]	$150
1378001	37800-1	Medroxyprogesterone Acetate (200 mg)	H-2		H-1 (04/03)	[71-58-9]	$150

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1379004	37900-4	Medrysone (500 mg)	F			[2668-66-8]	$150
1379605	37960-5	Mefenamic Acid (200 mg)	F3A032		F-2 (01/03)	[61-68-7]	$150
1379106	37910-6	Megestrol Acetate (500 mg)	I		H (05/00)	[595-33-5]	$150
1379300	37930-0	Melphalan Hydrochloride (200 mg)	G			[3223-07-2]	$150
1381006	38100-6	Menadione (200 mg) (Vitamin K3)	H-3		H-2 (02/00)	[58-27-5]	$150
1381709	38170-9	Menthol (250 mg)	I0B049		H (04/03)	[2216-51-5]	$150
1381742	38174-2	Menthyl Anthranilate (500 mg/ampule)	F0B103			[134-09-8]	$150
1382009	38200-9	Mepenzolate Bromide (200 mg)	F			[76-90-4]	$150
1383001	38300-1	Meperidine Hydrochloride **CII** (200 mg)	I		H-1 (12/99)	[50-13-5]	$199
1384004	38400-4	Mephentermine Sulfate (250 mg)	F-1			[1212-72-2]	$150
1385007	38500-7	Mephenytoin (250 mg)	G			[50-12-4]	$150
1386000	38600-0	Mephobarbital **CIV** (250 mg)	G		F (01/01)	[115-38-8]	$199
1387002	38700-2	Mepivacaine Hydrochloride (200 mg)	H		G-4 (02/99)	[1722-62-9]	$150
1388005	38800-5	Meprednisone (200 mg)	G			[1247-42-3]	$150
1389008	38900-8	Meprobamate **CIV** (200 mg)	G-1		G (03/02)	[57-53-4]	$199
1390007	39000-7	Meprylcaine Hydrochloride (200 mg)	F			[956-03-6]	$150
1391000	39100-0	3-Mercapto-2-methylpropanoic Acid 1,2-Diphenylethylamine Salt (75 mg)	G			n/f	$468
1392002	39200-2	Mercaptopurine (500 mg)	I-1		I (07/02) H (12/99)	[6112-76-1]	$150
1392705	39270-5	Mesalamine (200 mg)	G1B001		G (01/03) F-1 (03/00)	[89-57-6]	$150
1393005	39300-5	Mesoridazine Besylate (250 mg)	I-1			[32672-69-8]	$150
1394008	39400-8	Mestranol (200 mg)	J		I-1 (09/99)	[72-33-3]	$150
1395500	39550-0	Metaproterenol Sulfate (200 mg)	F-3			[5874-97-5]	$150
1396003	39600-3	Metaraminol Bitartrate (200 mg)	F-3			[33402-03-8]	$150
1396400	39640-0	Methacrylic Acid Copolymer Type A (200 mg)	G0B140		F-2 (04/03)	n/f	$150
1396502	39650-2	Methacrylic Acid Copolymer Type B (200 mg)	G0B141		F-2 (04/03)	n/f	$150
1396604	39660-4	Methacrylic Acid Copolymer Type C (100 mg)	G1B088		G (08/03)	n/f	$119
1397006	39700-6	Methacycline Hydrochloride (200 mg)	H		G (04/01)	[3963-95-9]	$150
1398009	39800-9	Methadone Hydrochloride **CII** (200 mg)	I0B163		H-1 (08/03)	[1095-90-5]	$199
1399001	39900-1	Methamphetamine Hydrochloride **CII** (125 mg)	I			[51-57-0]	$199
1401001	40100-1	Methantheline Bromide (200 mg)	F-1			[53-46-3]	$150
1402004	40200-4	Methapyrilene Fumarate (200 mg)	F-1			[33032-12-1]	$150
1404000	40400-0	Methaqualone **CI** (500 mg)	F-1			[72-44-6]	$199
1405002	40500-2	Metharbital **CIII** (200 mg)	F-2		F-1 (07/99)	[50-11-3]	$199
1406005	40600-5	Methazolamide (500 mg)	G-1			[554-57-4]	$150
1407008	40700-8	Methdilazine (200 mg)	F-1			[1982-37-2]	$150
1408000	40800-0	Methdilazine Hydrochloride (200 mg)	G			[1229-35-2]	$150
1409003	40900-3	Methenamine (500 mg)	G			[100-97-0]	$150
1409502	40950-2	Methenamine Hippurate (200 mg)	F			[5714-73-8]	$150
1409604	40960-4	Methenamine Mandelate (200 mg)	F-2		F-1 (11/00)	[587-23-5]	$150
1410002	41000-2	Methicillin Sodium (500 mg)	I1B186		I (03/03) H (03/00)	[7246-14-2]	$150
1411005	41100-5	Methimazole (200 mg)	G		F (02/01)	[60-56-0]	$150
1411504	41150-4	L-Methionine (200 mg)	G		F-2 (11/99)	[63-68-3]	$150
1412008	41200-8	Methocarbamol (200 mg)	H-1			[532-03-6]	$150
1413000	41300-0	Methohexital **CIV** (500 mg)	F-2			[18652-93-2]	$199
1414003	41400-3	Methotrexate (500 mg)	I			[59-05-2]	$150

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1415006	41500-6	Methotrimeprazine (125 mg)	F-2		F-1 (05/99)	[60-99-1]	$119
1416009	41600-9	Methoxamine Hydrochloride (200 mg)	F			[61-16-5]	$150
1417001	41700-1	Methoxsalen (500 mg)	H			[298-81-7]	$150
1418004	41800-4	Methoxyflurane (1 mL)	G			[76-38-0]	$150
1419007	41900-7	Methoxyphenamine Hydrochloride (250 mg)	F			[5588-10-3]	$150
1420006	42000-6	3-Methoxytyrosine (50 mg)	H			[300-48-1]	$468
1421009	42100-9	Methscopolamine Bromide (200 mg)	G			[155-41-9]	$150
1422001	42200-1	Methsuximide (500 mg)	F-2		F-1 (08/99)	[77-41-8]	$150
1424007	42400-7	Methyclothiazide (200 mg)	G			[135-07-9]	$150
1424018	42401-8	Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide)	G		F-2 (12/00)	n/f	$468
1424222	42422-2	Methyl Benzylidene Camphor (200 mg)	F0B118			[36861-47-9]	$150
1424233	42423-3	Methyl Caprate (300 mg)	F			[110-42-9]	$150
1424244	42424-4	Methyl Caproate (300 mg)	F			[106-70-7]	$150
1424255	42425-5	Methyl Caprylate (300 mg)	F			[111-11-5]	$150
1424506	42450-6	Methylcellulose (1 g) (AS)	G0B222		F-2 (05/03)	[9004-67-5]	$150
1425000	42500-0	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) **(AS)** (STP)	F			[15589-00-1]	$199
1426002	42600-2	Methyldopa (500 mg)	I			[41372-08-1]	$150
1427005	42700-5	Methyldopate Hydrochloride (200 mg)	G-2			[2508-79-4]	$150
1428008	42800-8	Methylene Blue (250 mg)	G			[7220-79-3]	$150
1429000	42900-0	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) **(AS)** (MDA)	F-1			[6292-91-7]	$199
1430000	43000-0	Methylergonovine Maleate (50 mg) **(List Chemical)**	J		I (05/02)	[57432-61-8]	$150
1430305	43030-5	Methyl Laurate (500 mg)	F			[111-82-0]	$150
1430327	43032-7	Methyl Linoleate (5 x 50 mg)	F			[112-63-0]	$150
1430349	43034-9	Methyl Linolenate (5 x 50 mg)	F			[301-00-8]	$150
1430509	43050-9	3-O-Methylmethyldopa (50 mg)	G-1			n/f	$468
1431002	43100-2	Methyl 5-methyl-3-isoxazolecarboxylate (25 mg)	F-1		F (01/01)	[59-63-2]	$468
1431501	43150-1	Methyl Myristate (300 mg)	F			[124-10-7]	$150
1431556	43155-6	Methyl Oleate (500 mg)			F (04/04)	[112-62-9]	$150
1431603	43160-3	Methyl Palmitate (300 mg)	F			[112-39-0]	$150
1431625	43162-5	Methyl Palmitoleate (300 mg)	F			n/f	$150
1432005	43200-5	Methylparaben (125 mg)	J-1		J (03/03))	[99-76-3]	$119
1433008	43300-8	Methylphenidate Hydrochloride **CII** (125 mg)	I		H (05/01)	[298-59-9]	$159
1434000	43400-0	Methylphenidate Hydrochloride Erythro-Isomer **CII** (25 mg)	J0B294		I0A006 (09/03) H-1 (01/03) H (06/01)	[298-59-9]	$538
1434022	43402-2	Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride)	G		F-2 (10/99)	n/f	$468
1435003	43500-3	Methylprednisolone (200 mg)	H			[83-43-2]	$150
1436006	43600-6	Methylprednisolone Acetate (200 mg)	G-2		G-1 (02/00)	[53-36-1]	$150
1437009	43700-9	Methylprednisolone Hemisuccinate (200 mg)	H			[2921-57-5]	$150
1437508	43750-8	Methyl Stearate (300 mg)	F			[112-61-8]	$150
1438001	43800-1	Methyltestosterone **CIII** (200 mg)	J		I (11/01)	[58-18-4]	$199
1440003	44000-3	Methysergide Maleate (200 mg)	H			[129-49-7]	$150
1440808	44080-8	Metoclopramide Hydrochloride (500 mg)	G		F-2 (06/99)	[54143-57-6]	$150
1441006	44100-6	Metocurine Iodide (300 mg)	G			[7601-55-0]	$150
1441200	44120-0	Metolazone (200 mg)	G0B246		F-1 (05/03)	[17560-51-9]	$150
1441287	44128-7	Metoprolol Fumarate (200 mg)	F			[119637-66-0]	$150

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1441301	44130-1	Metoprolol Tartrate (200 mg)	H1B059		H (01/04) G-1 (11/99)	[56392-17-7]	$150
1441505	44150-5	Metrizamide (500 mg)	F			[31112-62-6]	$150
1442009	44200-9	Metronidazole (100 mg)	I			[443-48-1]	$150
1443001	44300-1	Metyrapone (200 mg)	H		G (06/01)	[54-36-4]	$150
1443205	44320-5	Metyrosine (200 mg)	F			[672-87-7]	$150
1443250	44325-0	Mexiletine Hydrochloride (200 mg)	F-2		F-1 (09/02)	[5370-01-4]	$150
1443307	44330-7	Mezlocillin Sodium (350 mg)	G			[59798-30-0]	$150
1443409	44340-9	Miconazole (200 mg)	G-1		G (07/02)	[22916-47-8]	$150
1443500	44350-0	Miconazole Nitrate (200 mg)	I		H (06/99)	[22832-87-7]	$150
1443850		Powdered Milk Thistle Extract (250 mg)	F0B321			[84604-20-6]	$250
1443908		Milrinone (500 mg)	F0C050			[78415-72-2]	$250
1443919		Milrinone Related Compound A (50 mg) (1,6-Dihydro-2-methyl-6-oxo(3,4'-bipyridine)-5-carboxamide)	F0C051			[80047-24-1]	$468
1444004	44400-4	Minocycline Hydrochloride (200 mg)			H-3 (04/04) H-2 (07/02)	[13614-98-7]	$150
1444208	44420-8	Minoxidil (125 mg)	H		G (05/99)	[38304-91-5]	$119
1444707	44470-7	Mitomycin (50 mg)	K		J (07/01)	[50-07-7]	$461
1445007	44500-7	Mitotane (500 mg)	F			[53-19-0]	$150
1445200	44520-0	Mitoxantrone Hydrochloride (400 mg)	H		G (03/01)	[70476-82-3]	$479
1445222	44522-2	Mitoxantrone Related Compound A Hydrochloride (30 mg) (8-amino-1,4-dihydroxy-5[[2-[(2-hydroxyethyl)amino]ethyl]amino]-9,10-anthracenedione Hydrochloride)	F-1		F (03/01)	n/f	$200
1445459	44545-9	Molindone Hydrochloride (500 mg)	F			[15622-65-8]	$150
1445470	44547-0	Mometasone Furoate (200 mg)	G0B073		F-1 (04/03) F (02/01)	[83919-23-7]	$150
1445481		Monensin Sodium (200 mg)	F0B293			[22373-78-0]	$150
1445506	44550-6	Monobenzone (200 mg)	F			[103-16-2]	$150
1445801	44580-1	Mono- and Di-acetylated Monoglycerides (200 mg)	F			[68990-54-5]	$150
1446000	44600-0	Monoglycerides (125 mg)	H			[68990-53-4]	$119
1446804	44680-4	Monostearyl Maleate (100 mg)	G		F-2 (04/00)	[2424-62-6]	$468
1446950	44695-0	Moricizine Hydrochloride (100 mg)	F			[29560-58-5]	$150
1447002	44700-2	Morphine Monohydrate **CII** (50 mg) (AS)	G			[6009-81-0]	$199
1448005	44800-5	Morphine Sulfate **CII** (500 mg)	L0B056		K (06/03) J-1 (07/00)	[6211-15-0]	$319
1448504	44850-4	Moxalactam Disodium (500 mg)	F-1			[64953-12-4]	$150
1448901	44890-1	Mupirocin (50 mg)	F-1		F (03/02)	[12650-69-0]	$150
1448923	44892-3	Mupirocin Lithium (100 mg)	G		F (02/01)	[73346-79-9]	$150
1449008	44900-8	Myristyl Alcohol (1 g)	G		F (02/02)	[112-72-1]	$150
1449518		Nabumetone (200 mg)	F0C072	1		[42924-53-8]	$150
1449700	44970-0	Nadolol (200 mg)	F-3		F-2 (04/02)	[42200-33-9]	$150
1450007	45000-7	Nafcillin Sodium (200 mg)	H			[7177-50-6]	$150
1450404	45040-4	Naftifine Hydrochloride (200 mg)	F			[65473-14-5]	$150
1451000	45100-0	Nalidixic Acid (200 mg)	G			[389-08-2]	$150
1452002	45200-2	Nalorphine Hydrochloride **CIII** (250 mg)	I			[57-29-4]	$199
1453005	45300-5	Naloxone (125 mg)	L0B124		K-1 (12/02) K (07/01)	[465-65-6]	$119
1453504	45350-4	Naltrexone (200 mg)	G1B039		G (02/03)	[16590-41-3]	$150
1453526	45352-6	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride)	F			n/f	$199

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1454008	45400-8	Nandrolone **CIII** (50 mg)	F-3			[434-22-0]	$538
1455000	45500-0	Nandrolone Decanoate **CIII** (250 mg)	I			[360-70-3]	$199
1456003	45600-3	Nandrolone Phenpropionate **CIII** (250 mg)	H			[62-90-8]	$199
1457006	45700-6	Naphazoline Hydrochloride (200 mg)	K			[550-99-2]	$150
1457301	45730-1	Naproxen (200 mg)	I-1		I (03/03) H-1 (01/01)	[22204-53-1]	$150
1457403	45740-3	Naproxen Sodium (200 mg)	I			[26159-34-2]	$150
1457505	45750-5	Natamycin (200 mg)	I		H (11/99)	[7681-93-8]	$150
1458009	45800-9	Neomycin Sulfate (200 mg)	L-2		L-1 (09/01) L (02/99)	[1405-10-3]	$150
1459001	45900-1	Neostigmine Bromide (200 mg)	G			[114-80-7]	$150
1460000	46000-0	Neostigmine Methylsulfate (200 mg)	I		H (07/00)	[51-60-5]	$150
1460500	46050-0	Netilmicin Sulfate (500 mg)	H		G (05/02)	[56391-57-2]	$150
1461003	46100-3	Niacin (200 mg)	H-1			[59-67-6]	$150
1462006	46200-6	Niacinamide (500 mg) (Vitamin B3)	M-1		M (02/01)	[98-92-0]	$150
1463304	46330-4	Nicotine Bitartrate Dihydrate (500 mg)	G		F (05/99)	[128758-70-3]	$150
1463508	46350-8	Nifedipine (125 mg)	J0B243	2	I-1 (04/04)	[21829-25-4]	$119
1463600	46360-0	Nifedipine Nitrophenylpyridine Analog (25 mg)	K		J (04/01)	n/f	$468
1463701	46370-1	Nifedipine Nitrosophenylpyridine Analog (25 mg)	K		J (07/02)	n/f	$468
1464001	46400-1	Nitrofurantoin (500 mg)	J		I-1 (11/02)	[67-20-9]	$150
1465004	46500-4	Nitrofurazone (200 mg)	H-1		H (09/01)	[59-87-0]	$150
1465503	46550-3	Nitrofurfural Diacetate (100 mg)	F-1			[92-55-7]	$468
1466007	46600-7	Nitrofurazone Related Compound A (500 mg) (5-Nitro-2-furfuraldazine)	H0B100		G (07/03)	n/f	$468
1466506	46650-6	Diluted Nitroglycerin (5 ampules, approx. 200 mg of a 0.948% solution in propylene glycol each)	G			[55-63-0]	$150
1467804	46780-4	Nizatidine (200 mg)	G		F-1 (06/00)	[76963-41-2]	$150
1467950	46795-0	Nonoxynol 9 (0.5 mL)	H-1		H (03/02)	[26027-38-3]	$150
1468002	46800-2	Nonoxynol 10 (200 mg)	F			[26027-38-3]	$150
1468400	46840-0	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)	H1B035		H (03/03) G (03/00)	[1088-11-5]	$538
1468501	46850-1	Norepinephrine Bitartrate (125 mg)	H			[69815-49-2]	$119
1469005	46900-5	Norethindrone (200 mg)	J1B065		J-1 (05/03) J (07/02) I-1 (03/01)	[68-22-4]	$150
1470004	47000-4	Norethindrone Acetate (100 mg)	J0B072		I (04/03) H (06/99)	[51-98-9]	$150
1471007	47100-7	Norethynodrel (200 mg)	G			[68-23-5]	$150
1471506	47150-6	Norfloxacin (200 mg)	H		G (04/01)	[70458-96-7]	$150
1471914		Norgestimate (200 mg)	F0C086	1		[35189-28-7]	$150
1472000	47200-0	Norgestrel (125 mg)	I		H (05/99)	[6533-00-2]	$119
1473002	47300-2	Noroxymorphone Hydrochloride **CII** (50 mg)	H			n/f	$538
1474005	47400-5	Nortriptyline Hydrochloride (200 mg)	I		H (04/00)	[894-71-3]	$150
1474504	47450-4	Noscapine (500 mg)	G			[128-62-1]	$150
1475008	47500-8	Novobiocin (200 mg)	G-2			[303-81-1]	$150
1476000	47600-0	Nylidrin Hydrochloride (200 mg)	F-2			[849-55-8]	$150
1477003	47700-3	Nystatin (200 mg)	N1B004		N (01/03)	[1400-61-9]	$150
1477900	47790-0	Octinoxate (500 mg) (Octyl Methoxycinnamate)	G0C024	2,8	F0B032 (12/03)	[5466-77-3]	$150
1477411	47741-1	Octocrylene (500 mg)			F0B104 (05/04)	[6197-30-4]	$150
1477502	47750-2	Octoxynol 9 (200 mg)	G		F-2 (07/00)	[9002-93-1]	$150

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1477808	47780-8	Octyldodecanol (200 mg)	G		F-1 (07/99)	[5333-42-6]	$150
1477943	47794-3	Octyl Salicylate (400 mg)	F0B091			[118-60-5]	$150
1478108	47810-8	Ofloxacin (200 mg)	F-2		F-1 (08/02)	[82419-36-1]	$150
1478505	47850-5	Omeprazole (200 mg)	H1B211	2	H (05/04) G-1 (04/02) G (09/01)	[73590-58-6]	$150
1479009	47900-9	Orphenadrine Citrate (200 mg)	G		F-4 (05/02)	[4682-36-4]	$150
1481000	48100-0	Oxacillin Sodium (200 mg)	J		I (03/02)	[7240-38-2]	$150
1481500	48150-0	Oxamniquine (200 mg)	F			[21738-42-1]	$150
1481703	48170-3	Oxamniquine Related Compound A (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-7-nitro-6-quinolinemethyl methanesulfonate)	F			n/f	$468
1481805	48180-5	Oxamniquine Related Compound B (25 mg) (1,2,3,4-tetrahydro-2-isopropylaminomethyl-5-nitro-6-quinolinemethanol)	F			n/f	$468
1482003	48200-3	Oxandrolone **CIII** (50 mg)	G0B220		F-4 (07/03)	[53-39-4]	$199
1482207		Oxaprozin (200 mg)	F0C115	1		[21256-18-8]	$150
1483006	48300-6	Oxazepam **CIV** (200 mg)	G-1		G (12/00)	[604-75-1]	$199
1483505	48350-5	Oxprenolol Hydrochloride (200 mg)	H			[6452-73-9]	$150
1484009	48400-9	Oxtriphylline (500 mg)	G			[4499-40-5]	$150
1485001	48500-1	Oxybenzone (150 mg)	H0B263		G (11/03) F-2 (12/99)	[131-57-7]	$150
1485103	48510-3	Oxybutynin Chloride (200 mg)	G-1		G (11/02)	[1508-65-2]	$150
1485114	48511-4	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)	G		F-2 (01/00)	[4335-77-7]	$468
1485191	48519-1	Oxycodone **CII** (200 mg)	I0B046		H (01/03) G-1 (01/01)	[76-42-6]	$199
1486004	48600-4	Oxymetazoline Hydrochloride (200 mg)	I			[2315-02-8]	$150
1487007	48700-7	Oxymetholone **CIII** (200 mg)	G1B247		G (10/03)	[434-07-1]	$199
1488000	48800-0	Oxymorphone **CII** (500 mg)	H0B214		G (03/03)	[76-41-5]	$199
1489002	48900-2	Oxyphenbutazone (1 g)	H			[7081-38-1]	$150
1490103	49010-3	Oxyquinoline Sulfate (200 mg)	F-1		F (07/02)	[134-31-6]	$150
1491004	49100-4	Oxytetracycline (200 mg)	I-1			[6153-64-6]	$150
1491300	49130-0	Oxytocin (5 vials, 46 USP units per vial)	F			[50-56-6]	$150
1491503	49150-3	Padimate O (300 mg)	H0B154		G (04/03)	[21245-02-3]	$150
1492007	49200-7	Palmitic Acid (500 mg)	I			[57-10-3]	$150
1493000	49300-0	Pamoic Acid (250 mg)	G-4		G-3 (01/03)	[130-85-8]	$150
1494057	49405-7	Pancreatin Amylase and Protease (2 g)	I		H (10/00)	[8049-47-6]	$150
1494079	49407-9	Pancreatin Lipase (2 g)	I		H-1 (03/01)	[8049-47-6]	$150
1494501	49450-1	Panthenol, Racemic (200 mg)	G		F-1 (02/00)	[16485-10-2]	$150
1494807	49480-7	Pantolactone (500 mg)	F			[599-04-2]	$468
1495005	49500-5	Papain (1 g)	H		G (12/01)	[9001-73-4]	$150
1496008	49600-8	Papaverine Hydrochloride (200 mg)	H			[61-25-6]	$150
1497000	49700-0	Paramethadione (500 mg)	G			[115-67-3]	$150
1498003	49800-3	Paramethasone Acetate (200 mg)	G		F-1 (05/01)	[1597-82-6]	$150
1498706	49870-6	Parbendazole (200 mg)	F			[14255-87-9]	$150
1499006	49900-6	Pargyline Hydrochloride (200 mg)	F-1			[306-07-0]	$150
1500003	50000-3	Paromomycin Sulfate (125 mg)	G		F-3 (01/01)	[1263-89-4]	$150
1500218		Paroxetine Hydrochloride (500 mg)	F0B288			[110429-35-1]	$150

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1500229		Paroxetine Related Compound A (20 mg) (trans-4-(p-methoxyphenyl)-3-[(3,4-methylenedioxy)phenoxy]methylpiperidine Hydrochloride)	F0B172			n/f	$468
1500230		Paroxetine Related Compound B (20 mg) (trans-4-phenyl-3-([(3,4-methylenedioxy)phenoxy]methylpiperidine acetate)	F0B189			n/f	$468
1500240		Paroxetine Related Compound C (25 mg) ((+)-trans-paroxetine Hydrochloride)	F0B192			[130855-30-0]	$468
1500400	50040-0	Parthenolide (25 mg)	F			[20554-84-1]	$150
1500502	50050-2	Particle Count Set (2 blanks and 2 suspensions)	I		H (09/02)	n/f	$468
1500808	50080-8	Penbutolol Sulfate (200 mg)	F			[38363-32-5]	$150
1501006	50100-6	Penicillamine (200 mg)	H1B164		H (01/04)	[52-67-5]	$150
1501108	50110-8	Penicillamine Disulfide (100 mg)	H		G (07/00)	[20902-45-8]	$468
1502009	50200-9	Penicillin G Benzathine (200 mg)	J			[41372-02-5]	$150
1502508	50250-8	Penicillin G Potassium (200 mg)	I		H (02/99)	[113-98-4]	$150
1502552	50255-2	Penicillin G Procaine (200 mg)	F-1		F (03/99)	[6130-64-9]	$150
1502701	50270-1	Penicillin G Sodium (200 mg)	L-3		L-2 (09/01)	[69-57-8]	$150
1504489	50448-9	Penicillin V (200 mg)	F			[87-08-1]	$150
1504503	50450-3	Penicillin V Potassium (200 mg)	G-1		G (06/00)	[132-98-9]	$150
1505007	50500-7	Pentazocine **CIV** (500 mg)	H		G-1 (11/00)	[359-83-1]	$199
1505506	50550-6	Pentetic Acid (100 mg)	F-1		F (09/01)	[67-43-6]	$150
1507002	50700-2	Pentobarbital **CII** (200 mg)	H-2		H-1 (08/02)	[76-74-4]	$199
1508901		Pentoxifylline (200 mg)	F0B202			[6493-05-6]	$150
1510007	51000-7	Pepsin (5 g)	F-2			[9001-75-6]	$150
1510801	51080-1	Perflubron (0.5 mL)			F (04/04)	[423-55-2]	$150
1510845	51084-5	Pergolide Mesylate (200 mg)	F			[66104-23-2]	$187
1510867	51086-7	Pergolide Sulfoxide (50 mg)	F0B014			[72822-01-6]	$187
1511000	51100-0	Perphenazine (200 mg)	J0B249		I (10/03)	[58-39-9]	$150
1511203	51120-3	Perphenazine Sulfoxide (100 mg)	G-1		G (07/02)	[10078-25-8]	$468
1512002	51200-2	Phenacemide (250 mg)	F			[63-98-9]	$150
1513005	51300-5	Phenacetin (500 mg)	H-1		H (09/00)	[62-44-2]	$150
1514008	51400-8	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)	H3A009		H-2 (02/03) H-1 (06/01)	[62-44-2]	$88
1515000	51500-0	Phenazopyridine Hydrochloride (200 mg)	G-4			[136-40-3]	$150
1516003	51600-3	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025		G (12/02)	[956-90-1]	$199
1516502	51650-2	Phendimetrazine Tartrate **CIII** (350 mg)	G		F (01/01)	[50-58-8]	$199
1517006	51700-6	Phenelzine Sulfate (200 mg)	G		F-1 (04/02)	[156-51-4]	$150
1517301	51730-1	D-Phenethicillin Potassium (200 mg)	F			n/f	$468
1517607	51760-7	L-Phenethicillin Potassium (200 mg)	F			n/f	$150
1520000	52000-0	Phenformin Hydrochloride (200 mg)	G			[834-28-6]	$150
1522006	52200-6	Phenindione (250 mg)	F			[83-12-5]	$150
1522301	52230-1	Pheniramine Maleate (100 mg)	F			[132-20-7]	$150
1523009	52300-9	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2			[1707-14-8]	$199
1524001	52400-1	Phenobarbital **CIV** (200 mg)	J			[50-06-6]	$199
1524908	52490-8	Phenolphthalein (250 mg)	F-3			[77-09-8]	$150
1525004	52500-4	Phenolsulfonphthalein (100 mg)	F-2			[143-74-8]	$150
1526007	52600-7	Phenoxybenzamine Hydrochloride (250 mg)	G			[63-92-3]	$150
1527000	52700-0	Phenprocoumon (200 mg)			F-1 (02/04)	[435-97-2]	$150
1528002	52800-2	Phensuximide (500 mg)	G		F-1 (03/01)	[86-34-0]	$150
1528501	52850-1	Phentermine Hydrochloride **CIV** (200 mg)	H0B309		G (08/03)	[1197-21-3]	$199
1529005	52900-5	Phentolamine Hydrochloride (300 mg)	F			[73-05-2]	$150

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1530004	53000-4	Phentolamine Mesylate (200 mg)	I			[65-28-1]	$150
1530503	53050-3	L-Phenylalanine (200 mg)	H		G (02/02)	[63-91-2]	$150
1530809	53080-9	Phenylbenzimidazole Sulfonic Acid (200 mg)	F			[27503-81-7]	$150
1531007	53100-7	Phenylbutazone (250 mg)	J0A008		I-1 (02/03)	[50-33-9]	$150
1533002	53300-2	Phenylephrine Hydrochloride (125 mg)	K		J (02/99)	[61-76-7]	$119
1533308	53330-8	5-Phenylhydantoin (100 mg)	F			[89-24-7]	$468
1533851	53385-1	Phenylpropanediol (100 mg)	F			n/f	$468
1533909	53390-9	Phenylpropanolamine Bitartrate (100 mg) **(List Chemical)**	F			[67244-90-0]	$150
1534005	53400-5	Phenylpropanolamine Hydrochloride (250 mg) **(List Chemical)**	J		I (02/02)	[154-41-6]	$150
1535008	53500-8	Phenytoin (200 mg)	I2B233	2	I-1 (03/04) I (04/01)	[57-41-0]	$150
1535507	53550-7	Phenytoin Sodium (200 mg)	H		G (05/99)	[630-93-3]	$150
1535019		Phenytoin Related Compound A (50 mg) (2,2-Diphenylglycine)	F0C155	1		[3060-50-2]	$468
1535700	53570-0	Phosphated Riboflavin (50 mg)	G			[6184-17-4]	$119
1537003	53700-3	Physostigmine Salicylate (200 mg)	H-1		H (06/00)	[57-64-7]	$150
1538006	53800-6	Phytonadione (500 mg) (Vitamin K1)	M-1		M (09/01)	[84-80-0]	$150
1538505	53850-5	Pilocarpine (300 mg)	F			[92-13-7]	$150
1538902	53890-2	Pilocarpine Hydrochloride (200 mg)	H			[54-71-7]	$150
1539009	53900-9	Pilocarpine Nitrate (200 mg)	I			[148-72-1]	$150
1539508	53950-8	Pimozide (200 mg)	G			[2062-78-4]	$150
1539701	53970-1	Pindolol (200 mg)	H-1			[13523-86-9]	$150
1541000	54100-0	Piperacetazine (250 mg)	F			[3819-00-9]	$150
1541500	54150-0	Piperacillin (500 mg)	H			[66258-76-2]	$150
1541703	54170-3	Piperazine Adipate (200 mg)	F			[142-88-1]	$150
1541805	54180-5	Piperazine Citrate (200 mg)	F			[144-29-6]	$150
1541907	54190-7	Piperazine Dihydrochloride (200 mg)	F			[142-64-3]	$150
1542003	54200-3	Piperazine Phosphate (200 mg)	F			[14538-56-8]	$150
1543006	54300-6	Piperidolate Hydrochloride (200 mg)	F			[129-77-1]	$150
1544508	54450-8	Piroxicam (200 mg)	H		G (01/99)	[36322-90-4]	$150
1545205	54520-5	Plicamycin (50 mg)	H		G (04/00)	[18378-89-7]	$461
1545409	54540-9	Polacrilex Resin (100 mg)	F			n/f	$150
1545500	54550-0	Polacrilin Potassium (200 mg)	F-2		F-1 (09/00)	n/f	$150
1546106		Poloxalene (500 mg)	F0C009			[9003-11-6]	$150
1546300	54630-0	Polydimethylsiloxane (500 mg)	G-5		G-4 (06/01)	[9016-00-6]	$150
1546707	54670-7	Polyethylene, High Density (3 strips)	G		F-1 (04/01)	[9002-88-4]	$150
1546809	54680-9	Polyethylene, Low Density (3 strips)	G		F-2 (12/99)	[9002-88-4]	$150
1546853	54685-3	Polyethylene Oxide (100 mg)	F-1			[25322-68-3]	$150
1546900	54690-0	Polyethylene Terephthalate (PET) (3 Strips)	F			[25038-59-9]	$150
1546922	54692-2	Polyethylene Terephthalate G (PETG) (3 Strips)	F			[25640-14-6]	$150
1547007	54700-7	Polymyxin B Sulfate (200 mg)	K		J-1 (09/99)	[1405-20-5]	$150
1547404	54740-4	Polyoxyl 50 Stearate (200 mg)	F			[9004-99-3]	$150
1547903	54790-3	Polyoxyl 40 Stearate (200 mg)	F-2		F-1 (05/00)	[9004-99-3]	$150
1548000	54800-0	Polythiazide (200 mg)	F-1			[346-18-9]	$150
1550001	55000-1	Potassium Gluconate (200 mg)	G			[299-27-4]	$150
1551004	55100-4	Potassium Guaiacolsulfonate (500 mg)	J0B292		I-1 (07/03) I (11/00)	[78247-49-1]	$150

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Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1551150	55115-0	Potassium Sucrose Octasulfate (300 mg)	I0B283	2	H0B119 (04/04) G-1 (04/03) G (02/01)	[76578-81-9]	$150
1551300	55130-0	Potassium Trichloroammineplatinate (20 mg)	H0B149		G-1 (01/03) G (07/99)	[13820-91-2]	$468
1551503	55150-3	Povidone (100 mg)	F-1		F (11/01)	[9003-39-8]	$150
1553000	55300-0	Pralidoxime Chloride (200 mg)	G-2		G-1 (03/01) G (08/99)	[51-15-0]	$150
1554002	55400-2	Pramoxine Hydrochloride (500 mg)	I		H (11/02)	[637-58-1]	$150
1554501	55450-1	Prazepam **CIV** (500 mg)	G0C066		F-1 (11/02)	[2955-38-6]	$199
1554603	55460-3	Praziquantel (200 mg)	G		F-3 (07/02) F-2 (09/00)	[55268-74-1]	$150
1554658	55465-8	Praziquantel Related Compound A (50 mg) (2-benzoyl-1,2,3,6,7,11b-hexahydro-4 *H*-pyrazino [2,1-*a*]isoquinolin-4-one)	F-1			n/f	$468
1554669	55466-9	Praziquantel Related Compound B (50 mg) (2-(cyclohexyl-carbonyl)-2,3,6,7-tetrahydro-4 H-pyrazino [2,1-a]isoquinolin-4-one)	F-2		F-1 (06/00)	n/f	$468
1554670	55467-0	Praziquantel Related Compound C (50 mg) (2-(N-formylhex-ahydrohippuroyl-1,2,3,4-tetrahydroisoquinolin-1-one)	F-2		F-1 (06/00)	n/f	$468
1554705	55470-5	Prazosin Hydrochloride (500 mg)	G-1		G (02/01)	[19237-84-4]	$150
1555005	55500-5	Prednisolone (200 mg)	M		L-1 (04/02)	[50-24-8]	$150
1556008	55600-8	Prednisolone Acetate (200 mg)	J		I-1 (02/02)	[52-21-1]	$150
1556507	55650-7	Prednisolone Hemisuccinate (125 mg)	H-1		H (02/99)	[2920-86-7]	$119
1558003	55800-3	Prednisolone Tebutate (200 mg)	F			[7681-14-3]	$150
1559006	55900-6	Prednisone (250 mg)	L		K-1 (01/02) K (02/00)	[53-03-2]	$150
1559505	55950-5	Prednisone Tablets (Dissolution Calibrator, Disintegrating) (30 tablets)	N		M (09/02) L (11/00)	[53-03-2]	$173
1561008	56100-8	Prilocaine Hydrochloride (200 mg)	F-2			[1786-81-8]	$150
1561507	56150-7	Primaquine Phosphate (200 mg)	F-1			[63-45-6]	$150
1562000	56200-0	Primidone (200 mg)	G		F-6 (04/99)	[125-33-7]	$150
1563003	56300-3	Probenecid (200 mg)	I0A011		H-1 (03/03)	[57-66-9]	$150
1563309	56330-9	Probucol (200 mg)	G		F-1 (01/02)	[23288-49-5]	$150
1563320	56332-0	Probucol Related Compound A (25 mg) (2,2',6,6'-tetra-*tert*-butyldiphenoquinone)	F-1			n/f	$468
1563331	56333-1	Probucol Related Compound B (25 mg) (4,4'-dithio-bis(2,6-di-*tert*-butylphenol))	F-2		F-1 (08/03)	n/f	$468
1563342	56334-2	Probucol Related Compound C (25 mg) (4-[(3,5-di-*tert*-butyl-2-hydroxyphenylthio)isopropylidenethio]-2,6-di-*tert*-butylphe-nol)	F-2		F-1 (05/00)	n/f	$468
1563502	56350-2	Procainamide Hydrochloride (200 mg)	H1B117		H (04/03)	[614-39-1]	$150
1564006	56400-6	Procaine Hydrochloride (200 mg)	H			[51-05-8]	$150
1565009	56500-9	Procarbazine Hydrochloride (200 mg)	F			[366-70-1]	$150
1566001	56600-1	Prochlorperazine Maleate (200 mg)	H-1			[84-02-6]	$150
1567004	56700-4	Procyclidine Hydrochloride (200 mg)	G			[1508-76-5]	$150
1568007	56800-7	Progesterone (200 mg)	H-5		H-4 (07/02)	[57-83-0]	$119
1568506	56850-6	L-Proline (200 mg)	F-2		F-1 (01/02)	[147-85-3]	$150
1569000	56900-0	Promazine Hydrochloride (200 mg)			G (10/03)	[53-60-1]	$150
1570009	57000-9	Promethazine Hydrochloride (500 mg)	K		J-1 (10/00)	[58-33-3]	$150
1570304	57030-4	Propafenone Hydrochloride (200 mg)	G		F-1 (01/01)	[34183-22-7]	$150
1570508	57050-8	Propantheline Bromide (200 mg)	I0A019		H (11/02)	[50-34-0]	$150

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1329505	32950-5	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)	G0B258		F-1 (12/03)	n/f	$468
1571001	57100-1	Proparacaine Hydrochloride (200 mg)	G			[5875-06-9]	$150
1573007	57300-7	Propoxycaine Hydrochloride (200 mg)	F			[550-83-4]	$150
1574000	57400-0	Propoxyphene Hydrochloride **CII** (1 g)	K			[1639-60-7]	$199
1575002	57500-2	Propoxyphene Napsylate **CII** (1 g)	H			[26570-10-5]	$199
1575206	57520-6	Propoxyphene Related Compound A (50 mg) (alpha-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride)	G-5			n/f	$468
1576005	57600-5	Propranolol Hydrochloride (200 mg)	H-1		H (09/01)	[318-98-9]	$150
1576504	57650-4	Propylene Carbonate (200 mg)	F			[108-32-7]	$150
1576708	57670-8	Propylene Glycol (1 mL)	I0C022	2	H (03/04) G (02/99)	[57-55-6]	$150
1576720	57672-0	Propylene Glycol Diacetate (250 mg)	F			[623-84-7]	$150
1576800	57680-0	Propyl Gallate (200 mg)	G-1		G (01/03)	[121-79-9]	$150
1577008	57700-8	Propylparaben (200 mg)	I		H (02/00)	[94-13-3]	$150
1578000	57800-0	Propylthiouracil (200 mg)	G		F-1 (01/00)	[51-52-5]	$150
1578500	57850-0	Prostaglandin A1 (25 mg)	H0B108		G (04/03)	[14152-28-4]	$509
1580002	58000-2	Protriptyline Hydrochloride (200 mg)	F-1			[1225-55-4]	$150
1581005	58100-5	Pseudoephedrine Hydrochloride (125 mg) **(List Chemical)**	J1B203		J (01/04) I (05/02)	[345-78-8]	$119
1581504	58150-4	Pseudoephedrine Sulfate (200 mg) **(List Chemical)**	G		F-2 (05/02)	[7460-12-0]	$150
1584003	58400-3	Pyrantel Pamoate (1 g)	I		H-1 (04/00)	[22204-24-6]	$150
1585006	58500-6	Pyrazinamide (200 mg)	G		F-2 (02/00)	[98-96-4]	$150
1586009	58600-9	Pyridostigmine Bromide (200 mg)	H			[101-26-8]	$150
1587001	58700-1	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P		O-1 (04/00)	[58-56-0]	$150
1588004	58800-4	Pyrilamine Maleate (200 mg)	I0B276		H (12/03)	[59-33-6]	$150
1589007	58900-7	Pyrimethamine (200 mg)	H		G (07/02)	[58-14-0]	$150
1592001	59200-1	Pyrvinium Pamoate (500 mg)	G			[3546-41-6]	$150
1592205	59220-5	Quazepam **CIV** (200 mg)	F			[36735-22-5]	$199
1592227	59222-7	Quazepam Related Compound A (30 mg) (7-Chloro-1-(2,2,2-trifluoroethyl)-5-(2-fluorophenyl)-1,3-dihydro-2H-1,4-benzodiazepine-2-one)	F			n/f	$468
1592409	59240-9	Quercetin (500 mg)	F0B015			[6151-25-3]	$150
1593004	59300-4	Quinacrine Hydrochloride (200 mg)	F-1			[6151-30-0]	$150
1593412		Quinapril Related Compound A (50 mg) (Ethyl[3S-[2(R*),3a,11a beta]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-alpha-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate)	F0C114	1		[103733-49-9]	$468
1593423		Quinapril Related Compound B (50 mg) (3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-,[3S-[2[R*(R*)],3R*]]-)	F0C116	1		[85441-60-7]	$468
1594007	59400-7	Quinethazone (1.5 g)	G			[73-49-4]	$150
1594506	59450-6	Quinic Acid (200 mg)	F			[77-95-2]	$150
1595000	59500-0	Quinidine Gluconate (200 mg)	H1A028		H (04/03)	[7054-25-3]	$150
1595509	59550-9	Quinidine Sulfate (500 mg)	H-1		H (12/99)	[6591-63-5]	$150
1597005	59700-5	Quinine Sulfate (200 mg)	H			[6119-70-6]	$150
1597504	59750-4	Quininone (50 mg)	G-1			[84-31-1]	$468
1598008	59800-8	3-Quinuclidinyl Benzilate (25 mg)	H		G (11/01)	[6581-06-2]	$495
1598303		Ramipril (200 mg)	F0C099	1		[87333-19-5]	$150

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1598314		Ramipril Related Compound A (20 mg) (5-[[2-(aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanine hemifumarate salt)	F0C100	1		[91224-69-0]	$468
1598405	59840-5	Ranitidine Hydrochloride (200 mg)	H0B268		G (01/04)	[66357-59-3]	$150
1598507	59850-7	Ranitidine Related Compound A (50 mg) (5-[[(2-aminoethyl)thio]methyl]-N,N-dimethyl-2-furanmethanamine hemifumarate)	H1B137		H (01/04) G (01/01)	[91224-69-0]	$468
1598609	59860-9	Ranitidine Related Compound B (50 mg) (N,N'-bis[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-2-nitro-1,1-ethenediamine)	G		F-4 (04/02)	[72126-78-4]	$468
1598700	59870-0	Ranitidine Related Compound C (50 mg) (N-[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]sulfinyl]ethyl]-N-methyl-2-nitro-1,1-ethenediamine)	I1B136		I (01/04) H (05/01)	[73851-70-4]	$468
1599000	59900-0	Rauwolfia Serpentina (15 g)	G			[8063-17-0]	$150
1600813		Repaglinide (200 mg)	F0B265			[135062-02-1]	$150
1600824		Repaglinide Related Compound A (50 mg) ((S)-3-Methyl-1-[2-(1-piperidinyl)phenyl]butylamine, N-acetyl-L-glutamate salt)	F0B267			n/f	$468
1600835		Repaglinide Related Compound B (50 mg) (3-Ethoxy-4-ethoxycarbonyl-phenylacetic acid)	F0B269			[99469-99-5]	$468
1600846		Repaglinide Related Compound C (25 mg) ((S)-2-Ethoxy-4-[2-[[2-phenyl-1-[2-(1-piperidinyl)phenyl]ethyl]amino]-2-oxoethyl] benzoic acid)	F0B271			[107362-12-9]	$468
1601000	60100-0	Reserpine (200 mg)	N			[50-55-5]	$150
1602003	60200-3	Resorcinol (200 mg)	H-1		H (04/01)	[108-46-3]	$150
1602706	60270-6	Ribavirin (200 mg)	H		G (08/01)	[36791-04-5]	$278
1603006	60300-6	Riboflavin (500 mg) (Vitamin B2)	M-1		M (11/00)	[83-88-5]	$150
1603800	60380-0	Rifabutin (50 mg)	G0B040		F (11/02)	[72559-06-9]	$150
1604009	60400-9	Rifampin (300 mg)	J		I (09/00)	[13292-46-1]	$150
1604202	60420-2	Rifampin Quinone (50 mg)	H		G (12/01)	[13983-13-6]	$150
1604600	60460-0	Rimexolone (100 mg)	F			[49697-38-3]	$150
1604701	60470-1	Ritodrine Hydrochloride (200 mg)	G-1			[23239-51-2]	$150
1606208	60620-8	Roxarsone (200 mg)	F			[121-19-7]	$150
1606503	60650-3	Rutin (100 mg)	F			[153-18-4]	$150
1607007	60700-7	Saccharin (200 mg)	G-3		G-2 (12/01)	[81-07-2]	$150
1608000	60800-0	Salicylamide (200 mg)	F-4		F-3 (05/03)	[65-45-2]	$150
1609002	60900-2	Salicylic Acid (125 mg)	J2B147		J-1 (08/03) J (10/02) I (07/99)	[69-72-7]	$119
1609501	60950-1	Salicylic Acid Tablets (Dissolution Calibrator, Non-disintegrating) (33 tablets)	O		N (02/02)	[69-72-7]	$150
1609807	60980-7	Salsalate (125 mg)	G			[552-94-3]	$119
1609829	60982-9	Saquinavir Mesylate (200 mg)	F0B008			[149845-06-7]	$150
1609831	60983-1	Saquinavir Related Compound A (25 mg) (N-*tert*-butyl-decahydro-2-[2(R)-hydroxy-4-phenyl-3(S)-[[N-(2-quinolylcarbonyl)-D-asparaginyl]amino]butyl]-(4aS,8aS)-isoquinoline-3(S)-carboxamide)	F0B009			n/f	$468
1610001	61000-1	Scopolamine Hydrobromide (250 mg)	J0B051		I-1 (01/03)	[6533-68-2]	$150
1611004	61100-4	Secobarbital **CII** (200 mg)	H			[76-73-3]	$199
1611900	61190-0	Selegiline Hydrochloride (200 mg)	G			[14611-52-0]	$150
1611955	61195-5	Selenomethionine (100 mg)	F0B006			[1464-42-2]	$150
1612007	61200-7	Sennosides (250 mg)	H1B223	2	H (04/04)	[81-27-6] (A) [128-57-4] (B)	$150

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1612506	61250-6	L-Serine (200 mg)	G		F-3 (11/00)	[56-45-1]	$150
1612608	61260-8	Silver Sulfadiazine (200 mg)	I		H (04/01)	[22199-08-2]	$150
1612630	61263-0	Silybin (50 mg)	F			[22888-70-6]	$150
1612641	61264-1	Silydianin (20 mg)	F			[29782-68-1]	$150
1612652	61265-2	Simethicone (50 g)	G		F (07/00)	[8050-81-5]	$150
1612700	61270-0	Simvastatin (200 mg)	H1B093		H (07/03) G (02/02) F-1 (05/99)	[79902-63-9]	$150
1612801	61280-1	Sisomicin Sulfate (500 mg)			H (04/04) G (10/00)	[53179-09-2]	$150
1613509	61350-9	Sodium Ascorbate (200 mg)	G-1			[134-03-2]	$150
1613600	61360-0	Sodium Butyrate (25 mg)	F			[156-54-7]	$150
1614002	61400-2	Sodium Fluoride (1 g)	H-1		H (05/01)	[7681-49-4]	$150
1614308	61430-8	Sodium Lactate (200 mg)	H		G (06/00)	[867-56-1]	$150
1614501	61450-1	Sodium Nitroprusside (500 mg)	H		G (11/99)	[13755-38-9]	$150
1614603	61460-3	Sodium Propionate (200 mg)	F-1		F (03/02)	[6700-17-0]	$150
1614669		Sodium Starch Glycolate (400 mg)	F0C087	1		[9063-38-1]	$150
1614705	61470-5	Sodium Stearyl Fumarate (200 mg)	G		F-2 (05/01)	[4070-80-8]	$150
1616008	61600-8	1,4-Sorbitan (200 mg)	I0A003		H (04/03) G (02/00)	[27299-12-3]	$150
1617000	61700-0	Sorbitol (125 mg)	H1B139		H (01/04)	[50-70-4]	$119
1618003	61800-3	Spectinomycin Hydrochloride (200 mg)	F-2			[22189-32-8]	$150
1619006	61900-6	Spironolactone (125 mg)	J-1			[52-01-7]	$119
1619505	61950-5	Squalane (500 mg)	G-1			[111-01-3]	$150
1620005	62000-5	Stanozolol **CIII** (200 mg)	F-3		F-2 (02/01)	[10418-03-8]	$199
1621008	62100-8	Stearic Acid (500 mg)	J		I (10/01)	[57-11-4]	$150
1622000	62200-0	Stearyl Alcohol (125 mg)	H-1		H (09/99)	[112-92-5]	$119
1623003	62300-3	Streptomycin Sulfate (200 mg)	J0B195		I (04/03)	[3810-74-0]	$150
1623502	62350-2	Succinylcholine Chloride (500 mg)	H			[71-27-2]	$150
1623604	62360-4	Succinylmonocholine Chloride (150 mg)	G		F-1 (02/01)	[71-27-2]	$468
1623626	62362-6	Sucralose (400 mg)	G0B028		F (04/03)	[56038-13-2]	$150
1623637	62363-7	Sucrose (100 mg)	H0B002		G-1 (03/03) G (05/99)	[57-50-1]	$150
1623648	62364-8	Sufentanil Citrate **CII** (25 mg)	H0B208		G (05/03) F-1 (04/02) F (09/99)	[60561-17-3]	$199
1623670	62367-0	Sulbactam (250 mg)	G		F-1 (05/00)	[68373-14-8]	$150
1623681	62368-1	Sulconazole Nitrate (200 mg)	F-1		F (05/02))	[61318-91-0]	$150
1623706	62370-6	Sulfabenzamide (200 mg)	G			[127-71-9]	$150
1623808	62380-8	Sulfacetamide (300 mg)	G-1			[144-80-9]	$150
1624006	62400-6	Sulfacetamide Sodium (500 mg)	I		H (08/01)	[6209-17-2]	$150
1624505	62450-5	Sulfachlorpyridazine (200 mg)	F			[80-32-0]	$150
1625009	62500-9	Sulfadiazine (200 mg)	I			[68-35-9]	$150
1626001	62600-1	Sulfadimethoxine (200 mg)	F-3		F-2 (03/99)	[122-11-2]	$150
1626500	62650-0	Sulfadoxine (200 mg)	F-2		F-1 (07/02)	[2447-57-6]	$150
1628007	62800-7	Sulfamerazine (1 g)	H			[127-79-7]	$150
1629000	62900-0	Sulfamethazine (1 g)	G-3			[57-68-1]	$150
1630009	63000-9	Sulfamethizole (200 mg)	F-3		F-2 (01/03)	[144-82-1]	$150
1631001	63100-1	Sulfamethoxazole (200 mg)	I-1		I (04/02)	[723-46-6]	$150

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1631500	63150-0	Sulfamethoxazole N4-glucoside (25 mg)	H		G (11/01)	n/f	$468
1632004	63200-4	Sulfanilamide (5 g)	O0B047		N (01/04)	[63-74-1]	$150
1633007	63300-7	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)	K0B133	2	J-1 (03/04) J (09/99)	[63-74-1]	$72
1633506	63350-6	Sulfanilic Acid (200 mg)	G		F-2 (09/00)	[121-57-3]	$468
1634000	63400-0	Sulfapyridine (200 mg)	H			[144-83-2]	$150
1635002	63500-2	Sulfapyridine Melting Point Standard (1 g) (Approximately 191 degrees)	J		I (07/00)	[144-83-2]	$88
1635206	63520-6	Sulfaquinoxaline (200 mg)	F0A005			[59-40-5]	$150
1636005	63600-5	Sulfasalazine (125 mg)	G-2		G-1 (06/99)	[599-79-1]	$119
1636504	63650-4	Sulfathiazole (350 mg)	H		G (08/00)	[72-14-0]	$150
1637008	63700-8	Sulfinpyrazone (200 mg)	G			[57-96-5]	$150
1638000	63800-0	Sulfisoxazole (200 mg)	J		I-1 (06/99)	[127-69-5]	$150
1639003	63900-3	Sulfisoxazole Acetyl (200 mg)	H-1			[80-74-0]	$150
1640002	64000-2	Sulfisoxazole Diolamine (500 mg)	F			[4299-60-9]	$150
1642008	64200-8	Sulindac (200 mg)	H		G-1 (12/01)	[38194-50-2]	$150
1642507	64250-7	Suprofen (200 mg)	F			[40828-46-4]	$150
1642700		Tacrine Hydrochloride (500 mg)	F0C119	1		[1684-40-8]	$150
1643000	64300-0	Talbutal **CIII** (250 mg)	F			[115-44-6]	$199
1643306	64330-6	Tamoxifen Citrate (200 mg)	H		G-2 (09/01) G-1 (05/00)	[54965-24-1]	$150
1643361		Taurine (100 mg)	F0C104	1		[107-35-7]	$150
1643408	64340-8	Temazepam **CIV** (200 mg)	G		F (12/99)	[846-50-4]	$199
1643500	64350-0	Terbutaline Sulfate (125 mg)	H		G (04/99)	[23031-32-5]	$119
1643703	64370-3	Terconazole (200 mg)	G-2		G-1(04/01) G (03/99)	[67915-31-5]	$150
1643805	64380-5	Terfenadine (200 mg)	H		G (12/99)	[50679-08-8]	$150
1643907	64390-7	Terfenadine Related Compound A (100 mg) (1-[4-(1,1-dimethylethyl)phenyl]-4-[4-(hydroxydiphenylmethyl)-1-piperidinyl]-1-butanone)	G			n/f	$468
1643929	64392-9	Terfenadine Related Compound B (50 mg) (Terfenadine-N-oxide)	F			n/f	$468
1644003	64400-3	Terpin Hydrate (750 mg)	G			[2451-01-6]	$150
1645006	64500-6	Testolactone **CIII** (125 mg)	F-1			[968-93-4]	$159
1646009	64600-9	Testosterone **CIII** (125 mg)	I			[58-22-0]	$159
1647001	64700-1	Testosterone Cypionate **CIII** (200 mg)	G-1		G (08/01)	[58-20-8]	$199
1648004	64800-4	Testosterone Enanthate **CIII** (200 mg)	J			[315-37-7]	$199
1649007	64900-7	Testosterone Propionate **CIII** (200 mg)	L		K-1 (11/01)	[57-85-2]	$199
1650006	65000-6	Tetracaine Hydrochloride (200 mg)	J			[136-47-0]	$150
1651009	65100-9	Tetracycline Hydrochloride (200 mg)	K			[64-75-5]	$150
1652001	65200-1	Tetrahydrozoline Hydrochloride (200 mg)	G1A015		G (03/03)	[522-48-5]	$150
1652500		Thalidomide (200 mg)	F0C107	1		[50-35-1]	$175
1653004	65300-4	Theophylline (200 mg)	J0B180		I (01/04)	[58-55-9]	$150
1653106	65310-6	Theophylline Extended-Release Beads (Drug Release Calibrator, Multiple Unit) (20 g)	F-1			[58-55-9]	$150
1655000	65500-0	Thiabendazole (100 mg)	G0A027		F-1 (04/03) F (04/01)	[148-79-8]	$150
1656002	65600-2	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O		N (11/02) M-1 (04/99)	[67-03-8]	$150
1656308	65630-8	Thiamylal **CIII** (200 mg)	F			[77-27-0]	$199
1657005	65700-5	Thiethylperazine Malate (200 mg)	G		F-1 (09/00)	[52239-63-1]	$150

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1658008	65800-8	Thiethylperazine Maleate (200 mg)	F-1			[1179-69-7]	$150
1659000	65900-0	Thimerosal (500 mg)	H		G (12/99)	[54-64-8]	$150
1660000	66000-0	Thioguanine (200 mg)	F-1			[154-42-7]	$150
1661002	66100-2	Thiopental **CIII** (250 mg)	I			[76-75-5]	$199
1662504	66250-4	Thioridazine (200 mg)	H			[50-52-2]	$150
1663008	66300-8	Thioridazine Hydrochloride (200 mg)	H			[130-61-0]	$150
1663700	66370-0	Thiostrepton (200 mg)	F1B022		F (11/02)	[1393-48-2]	$150
1664000	66400-0	Thiotepa (500 mg)	I		H (01/99)	[52-24-4]	$150
1665003	66500-3	Thiothixene (250 mg)	G			[3313-26-6]	$150
1666006	66600-6	(E)-Thiothixene (100 mg)	H		G-1 (05/00)	[3313-27-7]	$468
1667100	66710-0	Thonzonium Bromide (200 mg)	F			[553-08-2]	$150
1667202	66720-2	L-Threonine (200 mg)	G		F-3 (12/00)	[72-19-5]	$150
1667279	66727-9	Thromboplastin, Human Recombinant (set) (1 vial Thromboplastin and 1 vial Diluent)	F			[9002-05-5]	$150
1667304	66730-4	Ticarcillin Monosodium Monohydrate (200 mg)	H		G-1 (03/99)	[74682-62-5]	$150
1667359		Tiletamine Hydrochloride (200 mg)	F0C019			[14176-50-2]	$150
1667406	66740-6	Timolol Maleate (200 mg)	G-1			[26921-17-5]	$150
1667520		Tinidazole (200 mg)	F0C093	1		[19387-91-8]	$150
1667530		Tinidazole Related Compound A (100 mg) (2-methyl-5-nitroimidazole)	F0C091	1		[696-23-1]	$468
1667439	66743-9	Tioconazole (200 mg)	H		G (04/02)	[65899-73-2]	$150
1667450	66745-0	Tioconazole Related Compound A (25 mg) (1-[2,4-Dichloro-beta-[(3-thenyl)-oxy]phenethyl]imidazole Hydrochloride)	G			n/f	$468
1667461	66746-1	Tioconazole Related Compound B (25 mg) (1-[2,4-Dichloro-beta-[(2,5-dichloro-3-thenyl)oxy]phenethyl]imidazole Hydrochloride)	G			n/f	$468
1667472	66747-2	Tioconazole Related Compound C (25 mg) (1-[2,4-Dichloro-beta-[(5-bromo-2-chloro-3-thenyl)-oxy]-phenethyl]imidazole Hydrochloride)	G			n/f	$468
1667508	66750-8	Tobramycin (250 mg)	K0B248		J (08/03)	[32986-56-4]	$150
1667552	66755-2	Tocainide Hydrochloride (125 mg)	F-1		F (04/99)	[35891-93-1]	$119
1667600	66760-0	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M		L-1 (01/00)	[10191-41-0]	$150
1667701	66770-1	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K		J (06/99)	[7695-91-2]	$150
1667803	66780-3	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)	F-5		F-4 (01/02)	[4345-03-3]	$150
1668001	66800-1	Tolazamide (200 mg)	G-2		G-1 (06/00)	[1156-19-0]	$150
1669004	66900-4	Tolazoline Hydrochloride (300 mg)	F			[59-97-2]	$150
1670003	67000-3	Tolbutamide (200 mg)	I		H (06/00)	[64-77-7]	$150
1670502	67050-2	Tolmetin Sodium (500 mg)	I0B064		H (09/03)	[64490-92-2]	$150
1671006	67100-6	Tolnaftate (200 mg)	I			[2398-96-1]	$150
1672009	67200-9	Toluenesulfonamides, ortho and para (200 mg of each supplied in a set)	F-4		F-3 (11/99)	[88-19-7] (o) [70-55-3] (p)	$468
1672304	67230-4	Torsemide (200 mg)	F0B090			[56211-40-6]	$150
1672315	67231-5	Torsemide Related Compound A (75 mg) (4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B071			n/f	$468
1672326	67232-6	Torsemide Related Compound B (75 mg) (N-[(n-butylamino)-carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B083			n/f	$468
1672337	67233-7	Torsemide Related Compound C (75 mg) (N-[(ethylamino)-carbonyl]-4-[(3-methylphenyl)amino]-3-pyridinesulfonamide)	F0B078			n/f	$468
1672803	67280-3	Transplatin (25 mg)	H0B287	2	G (03/04)	[14913-33-8]	$468

USP Reference Standards and Authentic Substances

Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1673500	67350-0	Trazodone Hydrochloride (200 mg)	F-2			[25332-39-2]	$150
1674004	67400-4	Tretinoin (30 mg/ampule; 5 ampules)	I2B185		I-1 (01/04) I (01/02) H (06/01)	[302-79-4]	$150
1675007	67500-7	Triacetin (1 g)	G-1		G (06/01)	[102-76-1]	$150
1676000	67600-0	Triamcinolone (250 mg)	H-1			[124-94-7]	$150
1677002	67700-2	Triamcinolone Acetonide (500 mg)	K		J (03/99)	[76-25-5]	$150
1678005	67800-5	Triamcinolone Diacetate (200 mg)	G			[67-78-7]	$150
1679008	67900-8	Triamcinolone Hexacetonide (125 mg)	G			[5611-51-8]	$119
1680007	68000-7	Triamterene (200 mg)	I			[396-01-0]	$150
1680506	68050-6	Triazolam **CIV** (200 mg)	H0B041		G-1 (03/03)	[28911-01-5]	$199
1680608	68060-8	Tributyl Citrate (500 mg)	F			[77-94-1]	$150
1680801	68080-1	Trichlorfon (200 mg)	F			[52-68-6]	$150
1681000	68100-0	Trichlormethiazide (200 mg)	H			[133-67-5]	$150
1682206		Triclosan (200 mg)	F0B135			[3380-34-5]	$150
1683005	68300-5	Tridihexethyl Chloride (200 mg)	F-1			[4310-35-4]	$150
1683504	68350-4	Trientine Hydrochloride (125 mg)	F2B257		F-1 (09/03) F (08/96)	[38260-01-4]	$119
1683606	68360-6	Triethyl Citrate (500 mg)	F-1		F (03/02)	[77-93-0]	$150
1685000	68500-0	Trifluoperazine Hydrochloride (200 mg)	H0A010		G (03/03)	[440-17-5]	$150
1685500	68550-0	2-[N-(2,2,2-Trifluoro-ethyl)amino-5]-chlorobenzophenone (25 mg)	F			n/f	$468
1686003	68600-3	Triflupromazine Hydrochloride (200 mg)	F-1			[1098-60-8]	$150
1686309	68630-9	Trifluridine (200 mg)	F			[70-00-8]	$150
1686310	68631-0	Trifluridine Related Compound A (20 mg) (5-Carboxy-2'-deoxyuridine)	F			[14599-46-3]	$468
1687006	68700-6	Trihexyphenidyl Hydrochloride (200 mg)	J		I (07/01)	[52-49-3]	$150
1689001	68900-1	Trimeprazine Tartrate (200 mg)	F-3		F-2 (08/01)	[4330-99-8]	$150
1690000	69000-0	Trimethadione (200 mg)	G			[127-48-0]	$150
1692006	69200-6	Trimethobenzamide Hydrochloride (500 mg)	H-2		H-1 (06/02)	[554-92-7]	$150
1692505	69250-5	Trimethoprim (300 mg)	J0B228		I (01/04)	[738-70-5]	$150
1693009	69300-9	Trioxsalen (200 mg)	G			[3902-71-4]	$150
1694001	69400-1	Tripelennamine Citrate (200 mg)	G		F (02/03)	[6138-56-3]	$150
1695004	69500-4	Tripelennamine Hydrochloride (200 mg)	J			[154-69-8]	$150
1696007	69600-7	Triprolidine Hydrochloride (500 mg)	I		H-1 (02/02)	[6138-79-0]	$150
1696109	69610-9	Triprolidine Hydrochloride Z-Isomer (100 mg)	G		F-1 (02/02)	n/f	$468
1696200	69620-0	Trisalicylic Acid (100 mg)	G		F-1 (10/99)	n/f	$468
1697000	69700-0	Troleandomycin (250 mg)	F-1			[2751-09-9]	$150
1698002	69800-2	Tromethamine (125 mg)	G		F-3 (07/99)	[77-86-1]	$119
1699005	69900-5	Tropicamide (125 mg)	G-1		G (02/99)	[1508-75-4]	$119
1700002	70000-2	Trypsin Crystallized (300 mg)	H		G (12/99)	[9002-07-7]	$150
1700501	70050-1	L-Tryptophan (200 mg)	G-1		G (09/00)	[73-22-3]	$150
1702008	70200-8	Tubocurarine Chloride (250 mg)	K-1			[6989-98-6]	$150
1703805		Tylosin (250 mg)	F0C008			[1401-69-0]	$150
1704003	70400-3	Tyloxapol (600 mg)	H		G (02/00)	[25301-02-4]	$150
1704502	70450-2	Tyropanoate Sodium (500 mg)	F			[7246-21-1]	$150
1705006	70500-6	L-Tyrosine (500 mg)	J			[60-18-4]	$150
1705301		Ubidecarenone (200 mg)	F0B191			[303-98-0]	$150
1705312		Ubidecarenone for System Suitability (25 mg)	F0B194			[303-98-0]	$150
1705505	70550-5	Undecylenic Acid (200 mg)	G-1		G (01/02)	[112-38-9]	$150

USP Reference Standards and Authentic Substances

Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1705800	70580-0	Uracil Arabinoside (50 mg)	G		F-1 (06/99)	[3083-77-0]	$150
1706009	70600-9	Uracil Mustard (500 mg)	F			[66-75-1]	$150
1706701		Urea C 13 (100 mg)	F0C078	1		[57-13-6]	$175
1707806	70780-6	Ursodiol (125 mg)	G		F-1 (11/01) F (09/99)	[128-13-2]	$119
1707908	70790-8	Valerenic Acid (25 mg)	G0B146		F (01/04)	[3569-10-6]	$669
1708503	70850-3	L-Valine (200 mg)	F-2		F-1 (05/02)	[72-18-4]	$150
1708707	70870-7	Valproic Acid (500 mg)	J1B127		J (01/04) I-1 (11/00)	[99-66-1]	$150
1708729	70872-9	Valproic Acid Related Compound A (0.25 mL) (diallylacetic acid)	F1B156		F (01/03)	[99-67-2]	$200
1709007	70900-7	Vancomycin Hydrochloride (4 vials, each vial contains 100,500 mcg of vancomycin activity)	L		K (08/01)	[1404-93-9]	$150
1710006	71000-6	Vanillin (200 mg)	I		H (04/99)	[121-33-5]	$150
1711009	71100-9	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)	J		I-1 (03/03) I (11/00)	[121-33-5]	$88
1711166		Vecuronium Bromide Related Compound A (25 mg) (3alpha, 17beta-diacetyl-oxy-2beta, 16beta-bispiperidinyl-5alpha-androstan)	F0B178			n/f	$468
1711202	71120-2	Verapamil Hydrochloride (200 mg)	G		F-4 (06/00)	[152-11-4]	$150
1711304	71130-4	Verapamil Related Compound A (50 mg) (3,4-Dimethoxy-alpha-[3-(methylamino)propyl]-alpha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride)	H		G (01/01)	n/f	$468
1711406	71140-6	Verapamil Related Compound B (50 mg) (alpha-[2-[[2-(3,4-dimethoxyphenyl)-ethyl]methylamino]ethyl]-3,4-dimethoxy-alpha-(1-methylethyl)-benzeneacetonitrile monoHydrochloride)	G			[1794-55-4]	$468
1711472		Verteporfin Related Compound A (50 mg) ((+/-)18-Ethenyl-4,4a-dihydro-3,4-bis(methoxycarbonyl)-4a,8,14,19-tetramethyl-23H,25H-benzo[b]prophine-9,13-dipropanoic acid)	F0C167	1		n/f	$468
1711508	71150-8	Vidarabine (200 mg)	G-1			[24356-66-9]	$150
1713004	71300-4	Vinblastine Sulfate (50 mg/ampule)	L		K (05/99)	[143-67-9]	$340
1714007	71400-7	Vincristine Sulfate (50 mg/ampule)	O0B062		N (01/03) M (04/99)	[2068-78-2]	$461
1715000	71500-0	Viomycin Sulfate (200 mg)	F			[37883-00-4]	$150
1716002	71600-2	Vitamin A (24 capsules each containing vitamin A acetate in cottonseed oil)			U (04/04)	[127-47-9]	$150
1717504	71750-4	Vitamin D Assay System Suitability (1.5 g)	F			[67-97-0]	$150
1717708		Vitexin (30 mg)	F0C142	1		[3681-93-4]	$500
1719000	71900-0	Warfarin (200 mg)	H-2		H-1 (11/01)	[81-81-2]	$150
1719102	71910-2	Warfarin Related Compound A (50 mg) (3-(o-hydroxyphenyl)-5-phenyl-2-cyclohexen-1-one)	G1B111		G (01/04)	[37209-23-7]	$150
1720000	72000-0	Xanthanoic Acid (100 mg)	G-1		G (12/00)	[82-07-5]	$468
1720203	72020-3	Xanthone (100 mg)	F-1			[90-47-1]	$468
1720407	72040-7	Xylazine (200 mg)	F			[7361-61-7]	$150
1720429	72042-9	Xylazine Hydrochloride (200 mg)	F			[23076-35-9]	$150
1720600	72060-0	Xylitol (1 g)	G0B037		F-3 (11/02) F-2 (05/00)	[87-99-0]	$150
1721002	72100-2	Xylometazoline Hydrochloride (125 mg)	I0B101		H-1 (05/03)	[1218-35-5]	$119
1722005	72200-5	Xylose (1 g)	F			[58-86-6]	$150
1724000	72400-0	Yohimbine Hydrochloride (200 mg)	F			[65-19-0]	$150
1724306	72430-6	Zalcitabine (200 mg)	F			[7481-89-2]	$150

USP Reference Standards and Authentic Substances

Cat. No.	Former Cat. No.	Description	Curr. Lot	Change Code*	Previous Lot/Valid Use Date	CAS No.	Price
1724317		Zalcitabine Related Compound A (50 mg) (2',3'-Didehydro-2',3'-dideoxycytidine)	F0B234			[7481-88-1]	$468
1724500	72450-0	Zidovudine (400 mg)	G		F (09/01)	[30516-87-1]	$150
1724521	72452-1	Zidovudine Related Compound B (25 mg) (3'-chloro-3'-deoxythymidine)	G0B116		F-1 (03/03) F (06/01)	[25526-94-7]	$468
1724532	72453-2	Zidovudine Related Compound C (100 mg) (thymine)	F-1		F (09/01)	[65-71-4]	$468
1724656		Zileuton (150 mg)	F0C062	1		[111406-87-2]	$150
1724667		Zileuton Related Compound A (50 mg) (N-(1-Benzo[b]thien-2-ylethyl) urea)	F0B316			n/f	$468
1724678		Zileuton Related Compound B (50 mg) (2-(Benzo[b]thien-2-oyl)benzo[b]thiophene)	F0B313			n/f	$468
1724689		Zileuton Related Compound C (50 mg) (1-Benzo[b]thien-2-ylethanone)	F0B299			n/f	$468
1724805	72480-5	Zolazepam Hydrochloride (500 mg)	G0C023	2	F-1 (03/04) F (05/02)	[33754-49-3]	$150

CROSS REFERENCE LIST

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
	Melting Point Standard - Acetanilide (500 mg; approximately 114 degrees)	1004001	Acetanilide Melting Point Standard (500 mg) (Approximately 114 degrees)
02200-3	3-Amino-4-carboxamidopyrazole Hemisulfate (50 mg) **(Limit Test)**	1013024	Allopurinol Related Compound A (50 mg) (3-Amino-4-carboxamidopyrazole Hemisulfate)
	Vitamin C	1043003	Ascorbic Acid (1 g) (Vitamin C)
06300-0	5-Benzyl-3,6-dioxo-2-piperazineacetic Acid (250 mg) **(Limit Test)**	1043728	Aspartame Related Compound A (75 mg) (5-Benzyl-3,6-dioxo-2-piperazineacetic Acid)
11670-8	4-(4-Chlorophenyl)-2-pyrrolidinone (75 mg) **(Limit Test)**	1048222	Baclofen Related Compound A (50 mg) (4-(4-Chlorophenyl)-2-pyrrolidinone)
02250-2	4-Amino-6-chloro-1,3-benzenedisulfonamide (100 mg) **(Limit Test)**	1057507	Benzothiadiazine Related Compound A (100 mg) (4-Amino-6-chloro-1,3-benzenedisulfonamide)
61500-5	Sodium Taurocholate (20 g)	1071304	Bile Salts (10 g) (Sodium Taurocholate)
02610-6	3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) **(Limit Test)**	1078325	Bumetanide Related Compound A (25 mg) (3-Amino-4-phenoxy-5-sulfamoylbenzoic Acid)
46660-8	3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid (25 mg) **(Limit Test)**	1078336	Bumetanide Related Compound B (25 mg) (3-Nitro-4-phenoxy-5-sulfamoylbenzoic Acid)
	Melting Point Standard - Caffeine (1 g; approximately 236 degrees)	1086006	Caffeine Melting Point Standard (1 g) (Approximately 236 degrees)
	Vitamin B5	1087009	Calcium Pantothenate (200 mg) (Vitamin B5)
42430-2	3-O-Methylcarbidopa (50 mg)	1095517	Carbidopa Related Compound A (50 mg) (3-O-Methylcarbidopa)
02620-8	alpha-Aminopropiophenone Hydrochloride (50 mg) **(Limit Test)**	1096804	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)
11500-2	7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-oxide (25 mg) **(Limit Test)**	1110020	Chlordiazepoxide Related Compound A (25 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one 4-Oxide)
11550-1	2-Chloro-3,5-dimethyl-phenol (50 mg) **(Limit Test)**	1122722	Chloroxylenol Related Compound A (50 mg) (2-chloro-3,5-dimethylphenol)
02240-6	2-Amino-4-chlorophenol (50 mg) **(Limit Test)**	1130527	Chlorzoxazone Related Compound A (50 mg) (2-Amino-4-chlorophenol)
	Vitamin D3	1131009	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)
32720-4	3-Hydroxy-1-methylquinuclidinium Bromide (250 mg) **(Limit Test)**	1135021	Clidinium Bromide Related Compound A (250 mg) (3-Hydroxy-1-methylquinuclindinium Bromide)
02460-0	3-Amino-4-(2-chloro-phenyl)-6-nitrocarbostyril (25 mg) **(Limit Test)**	1140327	Clonazepam Related Compound A (25 mg) (3-Amino-4-(2-chlorophenyl)-6-nitrocarbostyril)
02380-0	2-Amino-2'-chloro-5-nitrobenzophenone (25 mg) **(Limit Test)**	1140338	Clonazepam Related Compound B (25 mg) (2-Amino-2'-chloro-5-nitrobenzophenone)
11650-4	(o-Chlorophenyl)diphenyl-methanol (25 mg) (Limit Test)	1141024	Clotrimazole Related Compound A (25 mg) ((o-chlorophenyl)diphenylmethanol)
	Vitamin B12	1152009	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)
15870-8	Cyclosporine U (25 mg) DISCONTINUED	1158650	Cyclosporine Resolution Mixture (25 mg)
00200-6	5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid (50 mg) (Limit Test)	1184027	Diatrizoic Acid Related Compound A (50 mg) (5-Acetamido-3-amino-2,4,6-triiodobenzoic Acid)
42420-0	2-Methylamino-5-chlorobenzophenone (25 mg) **(Limit Test)**	1185020	Diazepam Related Compound A (25 mg) (2-Methyl-amino-5-chlorobenzophenone)
	Vitamin D2	1239005	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)
1268820	Etoposide Related Compound A (25 mg) (4'-Demethylepipodophyllotoxin 9-[4,6-O-(R)-ethylidene-alpha-D-glucopyranoside) DISCONTINUED	1268852	Etoposide Resolution Mixture (30 mg)
07350-3	2-(4-Biphenylyl)propionic Acid (100 mg) **(Limit Test)**	1285760	Flurbiprofen Related Compound A (100 mg) (2-(4-Biphenylyl)propionic Acid)
	Vitamim Bc Vitamin M	1286005	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)

CROSS REFERENCE LIST

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
08650-5	Calcium Formyltetrahydrofolate (50 mg) **(AS)** (For Qualitiative Use Only)	1286027	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)
11510-4	2-Chloro-4-N-furfuryl-amino-5-sulfamolybenzoic acid (50 mg) **(Limit Test)**	1287020	Furosemide Related Compound A (50 mg) (2-Chloro-4-N-furfurylamino-5-sulfamoylbenzoic Acid)
11900-3	4-Chloro-5-sulfamoylanthranilic Acid (100 mg) **(Limit Test)**	1287030	Furosemide Related Compound B (100 mg) (4-Chloro-5-sulfamoylanthranilic Acid)
07500-4	4,4'-Bis[4-(p-chlorophenyl)-4-hydroxypiperidino]-butyrophenone (25 mg) (Limit Test)	1303013	Haloperidol Related Compound A (25 mg) (4,4-Bis[(4-p-chlorophenyl)-4-hydroxy-piperidino]-butyrophenone)
11230-0	p-Chlorobenzhydrylpiperazine (25 mg)	1333058	Hydroxyzine Related Compound A (25 mg) (p-Chlorobenzhydrylpiperazine)
33010-7	Hydroxypropyl Methylcellulose Phthalate (100 mg)	1335304	Hypromellose Phthalate (100 mg)
07480-1	N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoisophthalamide (50 mg) **(Limit Test)**	1344724	Iopamidol Related Compound A (50 mg) (N,N'-Bis-(1,3-dihydroxy-2-propyl)-5-amino-2,4,6-triiodoiso-phthalamide)
68800-9	3-(3,4,6-Trihydroxyphenyl)-alanine (50 mg) **(Limit Test)**	1361010	Levodopa Related Compound A (50 mg) (3-(3,4,6-Trihydroxyphenyl)-alanine)
02490-5	2-Amino-2',5-dichlorobenzophenone (25 mg) **(Limit Test)**	1370338	Lorazepam Related Compound B (25 mg) (2-Amino-2',5-dichlorobenzophenone)
11310-9	6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxaldehyde (25 mg) **(Limit Test)**	1370349	Lorazepam Related Compound C (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxaldehyde)
11320-0	6-Chloro-4-(o-chloro-phenyl)-2-quinazolinecarboxylic Acid (25 mg) **(Limit Test)**	1370350	Lorazepam Related Compound D (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazolinecarboxylic Acid)
11330-2	6-Chloro-4-(o-chloro-phenyl)-2-quinazoline Methanol (25 mg) **(Limit Test)**	1370360	Lorazepam Related Compound E (25 mg) (6-Chloro-4-(o-chlorophenyl)-2-quinazoline Methanol)
	Vitamin K3	1381006	Menadione (200 mg) (Vitamin K3)
02420-2	4-Amino-6-chloro-N-3-methyl-m-benzenedisulfonamide (100 mg) (Limit Test)	1424018	Methyclothiazide Related Compound A (100 mg) (4-amino-6-chloro-N-3-methyl-m-benzenedisulfonamide)
53350-1	alpha-Phenyl-2-piperidineacetic Acid Hydrochloride (50 mg) **(Limit Test)**	1434022	Methylphenidate Related Compound A (50 mg) (alpha-Phenyl-2-piperidineacetic Acid Hydrochloride)
	Vitamin B3	1462006	Niacinamide (500 mg) (Vitamin B3)
46600-7	5-Nitro-2-furfuraldazine (500mg)	1466007	Nitrofurazone Related Compound A (500 mg) (5-Nitro-2-furfuraldazine)
11400-0	7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (50 mg) **(Limit Test)**	1468400	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)
1477900	Octyl Methoxycinnamate (500 mg)	1477900	Octinoxate (500 mg) (Octyl Methoxycinnamate)
53180-1	Phenylcyclohexylglycolic Acid (100 mg) **(Limit Test)**	1485114	Oxybutynin Related Compound A (100 mg) (Phenylcyclohexylglycolic Acid)
49400-2	Pancreatin (2 g)	1494057	Pancreatin Amylase and Protease (2 g)
49400-2	Pancreatin (2 g)	1494079	Pancreatin Lipase (2 g)
	Melting Point Standard - Phenacetin (500 mg; approximately 135 degrees)	1514008	Phenacetin Melting Point Standard (500 mg) (Approximately 135 degrees)
	Vitamin K1	1538006	Phytonadione (500 mg) (Vitamin K1)
54500-1	Plastic, Negative Control	1546707	Polyethylene, High Density (3 strips)
1329505	9-Hydroxypropantheline Bromide (50 mg)	1329505	Propantheline Bromide Related Compound A (50 mg) (9-Hydroxypropantheline bromide)
21000-3	alpha-d-4-Dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (125 mg) **(Limit Test)**	1575206	Propoxyphene Related Compound A (50 mg) (alpha-d-4-dimethylamino-1,2-diphenyl-3-methyl-2-butanol Hydrochloride)
	Vitamin B6	1587001	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)
	Vitamin B2	1603006	Riboflavin (500 mg) (Vitamin B2)
	Melting Point Standard - Sulfanilamide (1 g; approximately 165 degrees)	1633007	Sulfanilamide Melting Point Standard (500 mg) (Approximately 165 degrees)
	Vitamin B1 Hydrochloride	1656002	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)
	Vitamin E Alcohol	1667600	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)

CROSS REFERENCE LIST

Former Cat. No.	Former Description/Cross Reference	Cat. No.	New Description
	Vitamin E Acetate	1667701	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)
	Vitamin E Acid Succinate	1667803	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)
	Melting Point Standard - Vanillin (1 g; approximately 82 degrees)	1711009	Vanillin Melting Point Standard (1 g) (Approximately 82 degrees)

DIETARY SUPPLEMENT REFERENCE STANDARDS AVAILABLE FROM USP

Cat. No.	Former Cat. No.	Description	Curr. Lot	Price
AMINO ACIDS				
1012509	01250-9	L-Alanine (200 mg)	F-2	$150
1021000	02100-0	Aminocaproic Acid (200 mg)	F-4	$150
1042500	04250-0	L-Arginine (200 mg)	G-1	$150
1042601	04260-1	Arginine Hydrochloride (125 mg)	G0B060	$119
1161509	16150-9	L-Cysteine Hydrochloride (200 mg)	H	$150
1294808		Glutamine (100 mg)	F0B244	$150
1294976		Glutamic Acid (200 mg)	F0C069	$150
1295800	29580-0	Glycine (200 mg)	F-3	$150
1308505	30850-5	L-Histidine (200 mg)	G0A018	$150
1349502	34950-2	L-Isoleucine (200 mg)	F-2	$150
1357001	35700-1	L-Leucine (200 mg)	H0B237	$150
1359903	35990-3	Levocarnitine (400 mg)	G0B197	$150
1359925	35992-5	Levocarnitine Related Compound A (100 mg) (3-carboxy-N,N,N-trimethyl-2-propen-1-aminium chloride)	F-1	$200
1371501	37150-1	L-Lysine Acetate (200 mg)	F	$150
1372005	37200-5	L-Lysine Hydrochloride (200 mg)	H	$150
1411504	41150-4	L-Methionine (200 mg)	G	$150
1530503	53050-3	L-Phenylalanine (200 mg)	H	$150
1568506	56850-6	L-Proline (200 mg)	F-2	$150
1612506	61250-6	L-Serine (200 mg)	G	$150
1667202	66720-2	L-Threonine (200 mg)	G	$150
1705006	70500-6	L-Tyrosine (500 mg)	J	$150
1708503	70850-3	L-Valine (200 mg)	F-2	$150
BOTANICALS				
ASAIN GINSENG				
1291708		Powdered Asian Ginseng Extract (1.5 g)	F0B289	$500
CAPSAICIN/CAPSICUM				
1091108	09110-8	Capsaicin (100 mg)	G-1	$150
1200600	20060-0	Dihydrocapsaicin (25 mg)	G0C071	$150
CHAMOMILE				
1040708	04070-8	Apigenin-7-glucoside (30 mg)	F	$468
CRANBERRY LIQUID				
1134368	13436-8	Citric Acid (200 mg)	F1B092	$150
1181302	18130-2	Dextrose (500 mg)	J-1	$119
1286504	28650-4	Fructose (125 mg)	I-2	$119
1374601	37460-1	Malic Acid (Racemic) (200 mg)	G0B158	$150
1594506	59450-6	Quinic Acid (200 mg)	F	$150
1617000	61700-0	Sorbitol (125 mg)	H1B139	$119
1623637	62363-7	Sucrose (100 mg)	H0B002	$150
FEVERFEW				
1500400	50040-0	Parthenolide (25 mg)	F	$150
GARLIC				
1012145	01214-5	Agigenin (25 mg)	F	$150
1012950	01295-0	Alliin (25 mg)	F	$1,466
1115556	11555-6	beta-Chlorogenin (20 mg)	F	$150
1294848	29484-8	gamma-Glutamyl-S-allyl-L-cysteine (25 mg)	F	$649
GARLIC FLUID EXTRACT				
1013057	01305-7	S-Allyl-L-Cysteine (25 mg)	F	$468

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GINGER				
1291504	29150-4	Powdered Ginger (500 mg)	F	$150
1606503	60650-3	Rutin (100 mg)	F	$150
GINKGO				
1592409	59240-9	Quercetin (500 mg)	F0B015	$150
HAWTHORN LEAF WITH FLOWER				
1335202	33520-2	Hyperoside (50 mg)	F	$822
1717708		Vitexin (30 mg)	F0C142	$500
LICORICE				
1295888		Glycyrrhizic Acid (25 mg)	F0C006	$468
MILK THISTLE				
1443850		Powdered Milk Thistle Extract (250 mg)	F0B321	$250
1612630	61263-0	Silybin (50 mg)	F	$150
1612641	61264-1	Silydianin (20 mg)	F	$150
SAW PALMETTO				
1424233	42423-3	Methyl Caprate (300 mg)	F	$150
1424244	42424-4	Methyl Caproate (300 mg)	F	$150
1424255	42425-5	Methyl Caprylate (300 mg)	F	$150
1430305	43030-5	Methyl Laurate (500 mg)	F	$150
1430327	43032-7	Methyl Linoleate (5 x 50 mg)	F	$150
1430349	43034-9	Methyl Linolenate (5 x 50 mg)	F	$150
1431501	43150-1	Methyl Myristate (300 mg)	F	$150
1431556	43155-6	Methyl Oleate (500 mg)		$150
1431603	43160-3	Methyl Palmitate (300 mg)	F	$150
1431625	43162-5	Methyl Palmitoleate (300 mg)	F	$150
1437508	43750-8	Methyl Stearate (300 mg)	F	$150
VALERIAN				
1707908	70790-8	Valerenic Acid (25 mg)	G0B146	$669
CHONDROITIN				
1133570		Chondroitin Sulfate Sodium (300 mg)	F0B256	$150
OTHER DIETARY SUPPLEMENTS				
1133638	13363-8	Chromium Picolinate (100 mg)	F	$150
1150353	15035-3	Creatinine (100 mg)	F	$150
1611955	61195-5	Selenomethionine (100 mg)	F0B006	$150
VITAMINS-MINERALS				
1043003	04300-3	Ascorbic Acid (1 g) (Vitamin C)	Q0B012	$150
1071508	07150-8	Biotin (200 mg)	H1B019	$150
1086356	08635-6	Calcium Ascorbate (200 mg)	F-1	$150
1087009	08700-9	Calcium Pantothenate (200 mg) (Vitamin B5)	N-1	$150
1131009	13100-9	Cholecalciferol (30 mg/ampule; 5 ampules) (Vitamin D3)	M0B157	$153
1131803	13180-3	Delta-4,6-cholestadienol (30 mg)	F	$150
1152009	15200-9	Cyanocobalamin (1.5 g of mixture with mannitol; 10.7 mcg/mg of mixture) (Vitamin B12)	N	$150
1179504	17950-4	Dexpanthenol (500 mg)	I	$154
1239005	23900-5	Ergocalciferol (30 mg/ampule; 5 ampules) (Vitamin D2)	P0B275	$162
1241007	24100-7	Ergosterol (50 mg)	H	$150
1286005	28600-5	Folic Acid (500 mg) (Vitamin M or Vitamin Bc)	P	$150
1286027	28602-7	Folic Acid Related Compound A (50 mg) (Calcium Formyltetrahydrofolate)	I0B176	$150
1381006	38100-6	Menadione (200 mg) (Vitamin K3)	H-3	$150
1461003	46100-3	Niacin (200 mg)	H-1	$150

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1462006	46200-6	Niacinamide (500 mg) (Vitamin B3)	M-1	$150
1494501	49450-1	Panthenol, Racemic (200 mg)	G	$150
1494807	49480-7	Pantolactone (500 mg)	F	$468
1538006	53800-6	Phytonadione (500 mg) (Vitamin K1)	M-1	$150
1550001	55000-1	Potassium Gluconate (200 mg)	G	$150
1587001	58700-1	Pyridoxine Hydrochloride (200 mg) (Vitamin B6)	P	$150
1603006	60300-6	Riboflavin (500 mg) (Vitamin B2)	M-1	$150
1613509	61350-9	Sodium Ascorbate (200 mg)	G-1	$150
1614002	61400-2	Sodium Fluoride (1 g)	H-1	$150
1656002	65600-2	Thiamine Hydrochloride (500 mg) (Vitamin B1 Hydrochloride)	O	$150
1667600	66760-0	Alpha Tocopherol (250 mg) (Vitamin E Alcohol)	M	$150
1667701	66770-1	Alpha Tocopheryl Acetate (250 mg) (Vitamin E Acetate)	K	$150
1667803	66780-3	Alpha Tocopheryl Acid Succinate (250 mg) (Vitamin E Succinate)	F-5	$150
1716002	71600-2	Vitamin A (24 capsules each containing vitamin A acetate in cottonseed oil)		$150
1717504	71750-4	Vitamin D Assay System Suitability (1.5 g)	F	$150

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1012906	01290-6	Alfentanil Hydrochloride **CII** (500 mg)	F0B016	$199
1014005	01400-5	Alphaprodine Hydrochloride **CII** (250 mg)	F	$199
1015008	01500-8	Alprazolam **CIV** (200 mg)	H	$199
1030001	03000-1	Amobarbital **CII** (200 mg)	F-2	$199
1036008	03600-8	Anileridine Hydrochloride **CII** (250 mg)	F	$199
1042000	04200-0	Aprobarbital **CIII** (200 mg) (AS)	F-1	$199
1059003	05900-3	Benzphetamine Hydrochloride **CIII** (200 mg) (AS)	F-1	$199
1078700	07870-0	Buprenorphine Hydrochloride **CIII** (50 mg)	F-1	$199
1079000	07900-0	Butabarbital **CIII** (200 mg)	H0C007	$199
1081002	08100-2	Butalbital **CIII** (200 mg)	G2B077	$199
1082504	08250-4	Butorphanol Tartrate **CIV** (500 mg)	J	$199
1089004	08900-4	Cannabidiol **CI** (25 mg) (AS)	F-2	$199
1090003	09000-3	Cannabinol **CI** (25 mg) (AS)		$199
1096804	09680-4	Cathinone Hydrochloride **CI** (50 mg) (alpha-Aminopropiophenone Hydrochloride)	I	$538
1109000	10900-0	Chlordiazepoxide **CIV** (200 mg)	I0B063	$199
1110009	11000-9	Chlordiazepoxide Hydrochloride **CIV** (200 mg)	G-4	$199
1140305	14030-5	Clonazepam **CIV** (200 mg)	G1B175	$199
1140509	14050-9	Clorazepate Dipotassium **CIV** (125 mg)	G0B027	$199
1143008	14300-8	Cocaine Hydrochloride **CII** (250 mg)	I0B074	$199
1143802	14380-2	Codeine N-Oxide **CI** (50 mg)	G0A034	$199
1144000	14400-0	Codeine Phosphate **CII** (100 mg)	I-1	$199
1145003	14500-3	Codeine Sulfate **CII** (250 mg)	H-2	$199
1180004	18000-4	Dextroamphetamine Sulfate **CII** (500 mg)	H	$208
1183002	18300-2	Diacetylmorphine Hydrochloride **CI** (25 mg) **(AS)** (Heroin Hydrochloride)	J	$199
1185008	18500-8	Diazepam **CIV** (100 mg)	I	$199
1187207	18720-7	Dichloralphenazone **CIV** (200 mg)	F0B010	$199
1194009	19400-9	Diethylpropion Hydrochloride **CIV** (200 mg)	H	$199
1200804	20080-4	Dihydrocodeine Bitartrate **CII** (200 mg)	H	$199
1219008	21900-8	Diphenoxylate Hydrochloride **CII** (200 mg)	I	$199
1258305	25830-5	Ethchlorvynol **CIV** (0.7 ml)	F0B011	$199
1270005	27000-5	Fentanyl Citrate **CII** (100 mg)	J2B227	$199
1280009	28000-9	Fluoxymesterone **CIII** (200 mg)	G-2	$199
1285002	28500-2	Flurazepam Hydrochloride **CIV** (200 mg)	I	$199
1295006	29500-6	Glutethimide **CII** (500 mg)	F	$199
1302305	30230-5	Halazepam **CIV** (200 mg)	F	$199
1307003	30700-3	Hexobarbital **CIII** (500 mg)	F	$199
1315001	31500-1	Hydrocodone Bitartrate **CII** (250 mg)	J0A026	$199
1323000	32300-0	Hydromorphone Hydrochloride **CII** (50 mg)	I	$199
1356009	35600-9	Ketamine Hydrochloride **CIII** (250 mg)	G-2	$199
1359506	35950-6	Levmetamfetamine **CII** (75 mg)	F	$199
1362001	36200-1	Levo-alpha-acetylmethadol Hydrochloride **CII** (25 mg) (AS)		$199
1364007	36400-7	Levorphanol Tartrate **CII** (500 mg)	H	$199
1370305	37030-5	Lorazepam **CIV** (200 mg)	H0B023	$199
1371002	37100-2	Lysergic Acid Diethylamide Tartrate **CI** (10 mg) **(AS)** (LSD)	I	$199
1375309	37530-9	Mazindol **CIV** (350 mg)	H	$199
1383001	38300-1	Meperidine Hydrochloride **CII** (200 mg)	I	$199
1386000	38600-0	Mephobarbital **CIV** (250 mg)	G	$199
1389008	38900-8	Meprobamate **CIV** (200 mg)	G-1	$199
1398009	39800-9	Methadone Hydrochloride **CII** (200 mg)	I0B163	$199

CONTROLLED SUBSTANCES REFERENCE STANDARDS AVAILABLE FROM USP

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1399001	39900-1	Methamphetamine Hydrochloride **CII** (125 mg)	I	$199
1404000	40400-0	Methaqualone **CI** (500 mg)	F-1	$199
1405002	40500-2	Metharbital **CIII** (200 mg)	F-2	$199
1413000	41300-0	Methohexital **CIV** (500 mg)	F-2	$199
1425000	42500-0	4-Methyl-2,5-dimethoxyamphetamine Hydrochloride **CI** (25 mg) **(AS)** (STP)	F	$199
1429000	42900-0	Methylenedioxy-3,4-amphetamine Hydrochloride **CI** (25 mg) **(AS)** (MDA)	F-1	$199
1433008	43300-8	Methylphenidate Hydrochloride **CII** (125 mg)	I	$159
1434000	43400-0	Methylphenidate Hydrochloride Erythro-Isomer **CII** (25 mg)	J0B294	$538
1438001	43800-1	Methyltestosterone **CIII** (200 mg)	J	$199
1447002	44700-2	Morphine Monohydrate **CII** (50 mg) (AS)	G	$199
1448005	44800-5	Morphine Sulfate **CII** (500 mg)	L0B056	$319
1452002	45200-2	Nalorphine Hydrochloride **CIII** (250 mg)	I	$199
1453526	45352-6	Naltrexone Related Compound A **CII** (30 mg) (N-(3-butenyl)-noroxymorphone Hydrochloride)	F	$199
1454008	45400-8	Nandrolone **CIII** (50 mg)	F-3	$538
1455000	45500-0	Nandrolone Decanoate **CIII** (250 mg)	I	$199
1456003	45600-3	Nandrolone Phenpropionate **CIII** (250 mg)	H	$199
1468400	46840-0	Nordazepam **CIV** (50 mg) (7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one)	H1B035	$538
1473002	47300-2	Noroxymorphone Hydrochloride **CII** (50 mg)	H	$538
1482003	48200-3	Oxandrolone **CIII** (50 mg)	G0B220	$199
1483006	48300-6	Oxazepam **CIV** (200 mg)	G-1	$199
1485191	48519-1	Oxycodone **CII** (200 mg)	I0B046	$199
1487007	48700-7	Oxymetholone **CIII** (200 mg)	G1B247	$199
1488000	48800-0	Oxymorphone **CII** (500 mg)	H0B214	$199
1505007	50500-7	Pentazocine **CIV** (500 mg)	H	$199
1507002	50700-2	Pentobarbital **CII** (200 mg)	H-2	$199
1516003	51600-3	Phencyclidine Hydrochloride **CII** (25 mg) (AS)	G1B025	$199
1516502	51650-2	Phendimetrazine Tartrate **CIII** (350 mg)	G	$199
1523009	52300-9	Phenmetrazine Hydrochloride **CII** (200 mg)	F-2	$199
1524001	52400-1	Phenobarbital **CIV** (200 mg)	J	$199
1528501	52850-1	Phentermine Hydrochloride **CIV** (200 mg)	H0B309	$199
1554501	55450-1	Prazepam **CIV** (500 mg)	G0C066	$199
1574000	57400-0	Propoxyphene Hydrochloride **CII** (1 g)	K	$199
1575002	57500-2	Propoxyphene Napsylate **CII** (1 g)	H	$199
1592205	59220-5	Quazepam **CIV** (200 mg)	F	$199
1611004	61100-4	Secobarbital **CII** (200 mg)	H	$199
1620005	62000-5	Stanozolol **CIII** (200 mg)	F-3	$199
1623648	62364-8	Sufentanil Citrate **CII** (25 mg)	H0B208	$199
1643000	64300-0	Talbutal **CIII** (250 mg)	F	$199
1643408	64340-8	Temazepam **CIV** (200 mg)	G	$199
1645006	64500-6	Testolactone **CIII** (125 mg)	F-1	$159
1646009	64600-9	Testosterone **CIII** (125 mg)	I	$159
1647001	64700-1	Testosterone Cypionate **CIII** (200 mg)	G-1	$199
1648004	64800-4	Testosterone Enanthate **CIII** (200 mg)	J	$199
1649007	64900-7	Testosterone Propionate **CIII** (200 mg)	L	$199
1656308	65630-8	Thiamylal **CIII** (200 mg)	F	$199
1661002	66100-2	Thiopental **CIII** (250 mg)	I	$199
1680506	68050-6	Triazolam **CIV** (200 mg)	H0B041	$199

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Reference Standards; USP–NF (*Print or Electronic*); *Pharmacopeial Forum; USP Dictionary; Chromatographic Reagents*

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USA
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Fax: 703-605-6715
USP–NF (*Print or Electronic*)

Rittenhouse Book Distributors, Inc.
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USA
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Fax: 800-223-7488
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USP–NF (*Print*)

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Reference Standards

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PHARMACOPEIAL FORUM VOL. 29 NO. 5 **SEPT.–OCT. 2003**

* The *USP–NF* (*USP27–NF22*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

Please address comments on *PF* content to Executive Secretariat
USP–NF, 12601 Twinbrook Pkwy.
Rockville, MD 20852

Telephone: 1-301-816-8345
Fax: 1-301-816-8373
http://www.usp.org

Pharmacopeial Forum is covered in *Current Contents/Life Sciences* and in the *Science Citation Index (SCI),* in *International Pharmaceutical Abstracts*, and in *Current Awareness in Biological Sciences.*

The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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

STANDARDS DEVELOPMENT

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

USP publishes *Pharmacopeial Forum* (*PF*) bimonthly as the working vehicle of the USP Council of Experts. *PF* provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the *United States Pharmacopeia* and the *National Formulary* (*USP–NF*).

PF includes the following:

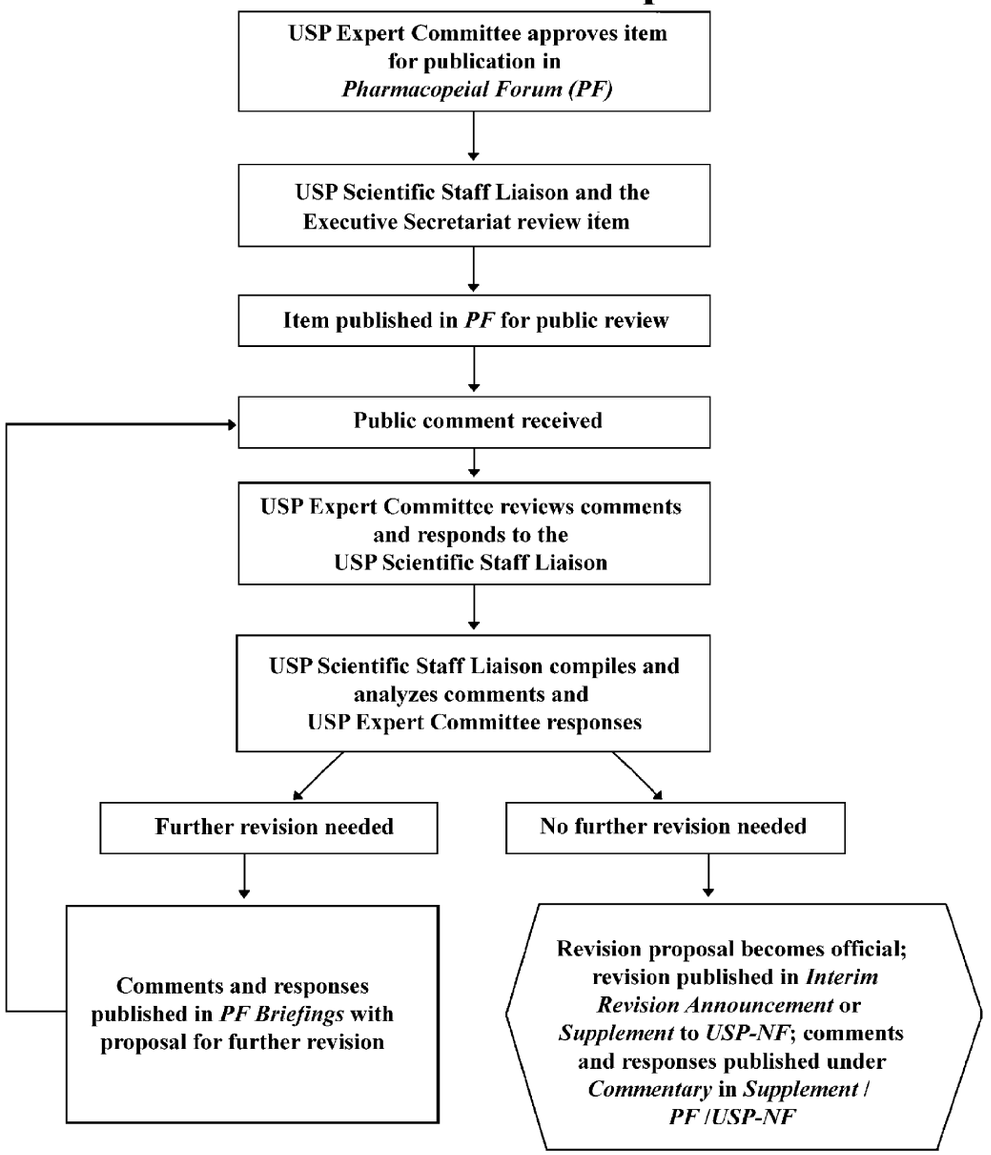
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official and binding before the publication of the next *USP–NF* or *Supplement* (*Interim Revision Announcement*)

USP welcomes comments and data on potential, proposed, or official standards.* Comments, along with USP's responses, will be published either in *PF Briefings*, the *Commentary* section of *PF*, the *Commentary* section of *Supplements* to *USP–NF*, or the *Commentary* section of *USP–NF*.

* If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before the section *Chromatographic Reagents Used in USP–NF and PF*.

The chart below shows the public review and comment process and its relationship to standards development.

Public Review and Comment Process for Standards Development



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

HOW TO USE *PF*

This section provides descriptions of the various parts of *PF*. It also includes *Committee Designations* and the *Staff Directory*.

The contents of the different sections of *PF* are briefly described below. Readers will get an idea of how each section is relevant to their job functions. They may contact USP scientific staff liaisons or staff members of the Executive Secretariat (listed in the *Staff Directory*) if they have any questions. A more detailed description of each section is provided at the beginning of that section.

Proposed and Adopted Revisions

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

Other Sections

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

Staff Directory
Names of all USP scientific staff liaisons with contact information.

Policies and Announcements
- General scientific and policy issues affecting *USP–NF* standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules

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

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

Index
Cumulative directory for the content of all issues of *PF* beginning with *PF* 29(1).

Reference Standards Catalog
List of official USP Reference Standards specified in *USP–NF*, along with availability and ordering information.

Chromatographic Reagents Used in USP–NF* and *Pharmacopeial Forum
Update of chromatographic reagents based on the proposals published in this issue of *PF*.

EXPERT COMMITTEE DESIGNATIONS*

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

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

* **HDQ** Indicates USP Headquarters items.
† The Expert Committee has been renamed. The old name, Excipients—Substances and Characterization (ESC) has been changed to Excipient Monograph Content (EMC).

STAFF DIRECTORY

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

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Andrzej Wilk, Senior Scientific Associate	aw@usp.org	(301) 816-8305	Pharmaceutical Analysis 5 (PA5); Radiopharmaceuticals and Medical Imaging (RMI)

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POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on *USP–NF* standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

PROPOSED NEW LABELING AND TESTING REQUIREMENTS FOR ACTIVE PHARMACEUTICAL INGREDIENTS INTENDED FOR USE IN FORMULATING INJECTABLE DOSAGE FORMS. Many monographs in the *USP* provide standards of quality for active pharmaceutical ingredients (API) that may be used in formulating injectable dosage forms. Therefore, it is proposed that any such active ingredient should be *labeled* to state either that it is sterile or that it must be subjected to further processing during the formulation of injectable dosage forms. Further, if it is labeled as sterile, it must meet the requirements for *Sterility* and *Bacterial endotoxins*. On the other hand, if the label states that it must be subjected to further processing during the formulation of injectable dosage forms, it must meet the requirements for *Bacterial endotoxins*.

Requirements such as these were adopted about ten yeas ago for a number of active antibiotic pharmaceutical ingredients labeled as "Sterile" or that had to be subjected to further processing during the formulation of injectable dosage forms. Therefore, these requirements are proposed to be applied to a number of active pharmaceutical ingredients. Proposals appearing in this issue of *PF* are presented in groups based on the USP Expert Committee responsible for them, specifically, PA1, PA4, and PA5. Proposals for other active pharmaceutical ingredients will appear in future issues of *PF*.

USP CONFERENCE ON BIOLOGICAL AND BIOTECHNOLOGICAL DRUG SUBSTANCES AND PRODUCTS, NOVEMBER 19–21, 2003.

This conference will be held in the Marriot Crystal City Gateway in Crystal City, Virginia. It is intended for those responsible for the development and maintenance of quality standards in this field. There are several objectives for this meeting:

- To involve industry and regulatory agencies in the development of quality standards for these products
- To promote the utility of standards for these products as necessary from regulatory and quality perspectives
- To involve stakeholders in the development of the future USP blueprint in these areas
- To promote the utility of USP as a neutral body bridging industry and the regulatory agencies for the benefit of public health.

This conference will consist of formal presentations and workshops led by nationally and internationally recognized experts in different areas of interest to the biological and biotechnological industry. Conference topics will include the following:

- Equivalence of biological and biotechnological drug substances and products
- Biotechnology-derived products
- Blood-derived products
- Vaccines
- Cell and gene therapy, and tissue engineering
- Bioassay
- Ancillary products.

For program information, contact Lokesh Bhattacharyya at 301-816-8201 or lb@usp.org. For conference registration information, call 301-816-8226, or register online at www.usp.org/conferences.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE *USP–NF*. We are pleased to announce the availability of the *USP Guideline for Submitting Requests for Revision to the USP–NF*. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-Complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

NEW *DIETARY SUPPLEMENTS* SECTION OF THE *USP*. As previously noted in earlier Announcements, beginning with *USP 27–NF 22*, all dietary supplement monographs will appear in the new *Dietary Supplements* section of the *USP*. Also, the section of *Pharmacopeial Forum* that was formerly entitled *Nutritional Supplements*

is being changed to *Dietary Supplements*. Monographs that formerly appeared in the *Nutritional Supplements* section will subsequently appear in the new *Dietary Supplements* section of the *USP* when they become official. Therefore, in addition to retaining the monographs that are in the current *Nutritional Supplements* section, the new section will include the following dietary supplement monographs that will be moved from the *NF*:

Chamomille
Choline Bitartrate
Choline Chloride
Chondroitin Sulfate Sodium
Chondroitin Sulfate Sodium Tablets
Chromium Picolinate
Cranberry Liquid Preparation
Echinacea angustifolia
Echinacea angustifolia, Powdered
Echinacea angustifolia, Powdered Extract
Echinacea pallida
Echinacea pallida, Powdered
Echinacea pallida, Powdered Extract
Echinacea purpurea Root
Echinacea purpurea Root, Powdered Extract
Echinacea purpurea, Powdered
Eleuthero
Eleuthero, Powdered
Eleuthero, Powdered Extract
Feverfew
Feverfew, Powdered
Garlic
Garlic Delayed-Release Tablets
Garlic Fluidextract
Garlic, Powdered
Garlic, Powdered Extract
Ginger
Ginger Tincture
Ginger, Powdered
Ginkgo
Ginseng, American
Ginseng, American, Powdered
Ginseng, American, Powdered Extract
Ginseng, Asian
Ginseng, Asian Tablets
Ginseng, Asian Powdered
Ginseng, Asian, Powdered Extract
Glucosamine and Chondroitin Sulfate Sodium Tablets
Glucosamine Hydrochloride
Glucosamine Sulfate Potassium Chloride
Glucosamine Sulfate Sodium Chloride
Glucosamine Tablets
Goldenseal
Goldenseal, Powdered
Goldenseal, Powdered Extract
Hawthorn Leaf with Flower
Hawthorn Leaf with Flower, Powdered
Horse Chestnut
Horse Chestnut, Powdered
Horse Chestnut, Powdered Extract
Licorice
Licorice, Powdered
Licorice, Powdered Extract
Lipoic Acid, Alpha
Lipoic Acid, Alpha Capsules
Lipoic Acid, Alpha Tablets
Milk Thistle
Milk Thistle Capsules
Milk Thistle Tablets
Milk Thistle, Powdered
Milk Thistle, Powdered Extract
Red Clover
Red Clover Tablets
Red Clover, Powdered
Red Clover, Powdered Extract
St. John's Wort
St. John's Wort, Powdered
St. John's Wort, Powdered Extract
Saw Palmetto
Saw Palmetto Capsules
Saw Palmetto Extract
Saw Palmetto, Powdered
Selenomethionine
Valerian
Valerian Tablets
Valerian, Powdered
Valerian, Powdered Extract

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Barbara B. Hubert, Director, Pharmacopeial Education, BBH@usp.org, 301-816-8333, or Diana Lenahan, Program Associate, DPL@usp.org, 301-816-8530. Call 301-816-8530 to get information on customized courses offered at USP or at your site.

Calendar of Pharmacopeial Education Courses, 2003

Date	Name of course	Location
September 15 and 16	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
September 18	Fundamentals of Microbiological Testing	USP Headquarters, Rockville, MD
September 24	Fundamentals of Titration	USP Headquarters, Rockville, MD
October 8	Analytical Method Validation	USP Headquarters, Rockville, MD
October 20 and 21	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
November 17 and 18	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
December 8	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 9	Standards 101: Advanced Use of *USP–NF*, General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
December 15 and 16	Fundamentals of Dissolution	USP Headquarters, Rockville, MD

VISIT THE USP WEB SITE AT ⟨http://www.usp.org⟩. Various resources related to Pharmacopeial standards are presented, including highlights from *PF*.

***USP–NF* AVAILABLE IN THREE ELECTRONIC FORMATS.** The trusted reference for official pharmaceutical standards is available in three convenient electronic formats—CD, intranet, and online. The CD is ideal for single users who prefer to have *USP–NF* on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official *USP–NF* content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

***CHROMATOGRAPHIC REAGENTS* NOW AVAILABLE.** *Chromatographic Reagents* lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in *Pharmacopeial Forum* (*PF*) since 1980. *Chromatographic Reagents* also helps to track which column reagents were used to validate methods that have become official and are included in *USP–NF*. The branded column reagents list is updated bimonthly through *Pharmacopeial Forum*. *Chromatographic Reagents* can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the
European Pharmacopoeia Commission
B.P. 907
F 67029 Strasbourg Cedex 1
France

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax. +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

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

Please note that *USP–NF* is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

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

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

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

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

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

PUBLICATION SCHEDULES

Publication	Publication Date	Official Date
1st Supplement	Feb. 2003	Apr. 1, 2003
PF 29(2) [Mar.–Apr. 2003]	Mar. 2003	Not Applicable
2nd IRA [published in *PF* 29(2)]	Mar. 2003	Apr. 1, 2003
PF 29(3) [May–June 2003]	May 2003	Not Applicable
3rd IRA [published in *PF* 29(3)]	May 2003	June 1, 2003
2nd Supplement	June 2003	Aug. 1, 2003
PF 29(4) [July–Aug. 2003]	July 2003	Not Applicable
4th IRA [published in *PF* 29(4)]	July 2003	Aug. 1, 2003
PF 29(5) [Sept.–Oct. 2003]	Sept. 2003	Not Applicable
5th IRA [published in *PF* 29(5)]	Sept. 2003	Oct. 1, 2003
PF 29(6) [Nov.–Dec. 2003]	Nov. 2003*	Not Applicable
6th IRA [published in *PF* 29(6)]	Nov. 2003*	Dec. 1, 2003*

* Tentative

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

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

Readers should review this section to determine if they are affected by any of the changes.

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ■new text■, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ■■, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement*, and ■2S (*USP 26*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 26*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 26–NF 21*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in the next available *Supplement*, and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

FIFTH INTERIM REVISION ANNOUNCEMENT to *USP 26* and to *NF 21*

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

Larry L. Braden, *Chair*
USP Board of Trustees

Roger L. Williams, *Executive Vice President*
and *Chairman, USP Council of Experts*

John W. Gasper, *Director*, *Executive Secretariat*

Official October 1, 2003. **Released September 1, 2003.**

All inquiries and comments regarding *USP 26* text and *NF 21* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were indicated in past *Supplements to USP–NF* as being not yet available, have since become available. Thus, the official date of each *USP 26* or *NF 21* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Acesulfame Potassium RS (January 1, 2004)
USP Alendronate Sodium RS (November 1, 2003)
USP Allantoin RS (March 1, 2004)
USP Amifostine Disulfide RS (March 1, 2004)
USP Aminopentamide Sulfate RS (September 1, 2003)
USP Amitraz RS (November 1, 2003)
USP Ammonium Chloride RS (March 1, 2004)
USP Powdered Asian Ginsing Extract RS (September 1, 2003)
USP Aspartame Acesulfame RS (March 1, 2004)
USP Betahistine Hydrochloride RS (January 1, 2004)
USP Brinzolamide RS (November 1, 2003)
USP Brinzolamide Related Compound A RS (November 1, 2003)
USP Brinzolamide Related Compound B RS (November 1, 2003)
USP Bupropion Hydrochloride RS (March 1, 2004)
USP Cefipime Hydrochloride RS (January 1, 2004)
USP Cefipime Hydrochloride System Suitability RS (January 1, 2004)
USP Cetyl Palmitate RS (November 1, 2003)
USP Choline Bitartrate RS (January 1, 2004)
USP Choline Chloride RS (March 1, 2004)
USP Chondroitin Sulfate Sodium RS (September 1, 2003)
USP Clozapine RS (November 1, 2003)
USP Copovidone RS (March 1, 2004)
USP Desflurane Related Compound A RS (March 1, 2004)
USP Desogestrel RS (September 1, 2003)
USP Desogestrel Related Compound A RS (September 1, 2003)
USP Desogestrel Related Compound B RS (September 1, 2003)
USP Desogestrel Related Compound C RS (September 1, 2003)
USP Dextran V_o Marker RS (September 1, 2003)
USP Dextran 4 Calibration RS (November 1, 2003)
USP Dextran 10 Calibration RS (November 1, 2003)
USP Dextran 40 Calibration RS (November 1, 2003)
USP Dextran 70 Calibration RS (November 1, 2003)
USP Dextran 250 Calibration RS (November 1, 2003)
USP Diloxanide Furoate RS (November 1, 2003)
USP Dinoprostone RS (November 1, 2003)
USP Dorzolamide RS (November 1, 2003)
USP Dorzolamide Hydrochloride Related Compound A RS (January 1, 2004)
USP Doxazosin Mesylate RS (March 1, 2004)
USP Emedastine Difumarate RS (November 1, 2003)
USP Ethinyl Estradiol Related Compound A RS (November 1, 2003)
USP Fenoldopam Mesylate RS (March 1, 2004)
USP Fenoldopam Related Compound A RS (January 1, 2004)
USP Fenoldopam Related Compound B RS (January 1, 2004)
USP Formononetin RS (March 1, 2004)
USP Fosphenytoin Sodium RS (March 1, 2004)
USP Gadoversetamide RS (March 1, 2004)
USP Gadoversetamide Related Compound A RS (March 1, 2004)
USP Gemfibrozil Related Compound A RS (January 1, 2004)
USP Glutamic Acid RS (November 1, 2003)
USP Glutamine RS (September 1, 2003)
USP Glycyrrhizic Acid RS (November 1, 2003)
USP Hydrocodone Bitartrate Related Compound A CII RS (March 1, 2004)
USP Hydroxypropyl Betadex RS (September 1, 2003)
USP Iodixanol RS (September 1, 2003)
USP Isoflupredone Acetate RS (January 1, 2004)
USP Powdered Kava Extract RS (March 1, 2004)
USP Kawain RS (March 1, 2004)
USP Ketamine Related Compound A RS (January 1, 2004)
USP Lansoprazole RS (November 1, 2003)
USP Lansoprazole Related Compound A RS (November 1, 2003)
USP Lynestrenol RS (September 1, 2003)
USP Meropenem RS (March 1, 2004)
USP Metformin Hydrochloride RS (March 1, 2004)
USP Metformin Related Compound A RS (March 1, 2004)
USP Powdered Milk Thistle Extract RS (November 1, 2003)
USP Milrinone RS (November 1, 2003)
USP Milrinone Related Compound A RS (November 1, 2003)
USP Monensin Sodium RS (September 1, 2003)
USP Nabumetone RS (January 1, 2004)
USP Norgestimate RS (January 1, 2004)
USP Ondansetron Hydrochloride RS (March 1, 2004)
USP Ondansetron Related Compound A RS (March 1, 2004)
USP Ondansetron Related Compound C RS (March 1, 2004)
USP Ondansetron Related Compound D RS (March 1, 2004)
USP Oxaprozin RS (January 1, 2004)
USP Oxfendazole RS (March 1, 2004)
USP Paclitaxel RS (March 1, 2004)
USP Paclitaxel Related Compound A RS (March 1, 2004)
USP Paclitaxel Related Compound B RS (March 1, 2004)
USP Paroxetine Hydrochloride RS (September 1, 2003)
USP Phenytoin Related Compound A RS (March 1, 2004)
USP Poloxalene RS (November 1, 2003)
USP Quinapril Related Compound A RS (January 1, 2004)
USP Quinapril Related Compound B RS (January 1, 2004)
USP Quinine Hydrochloride Dihydrate RS (March 1, 2004)
USP Ramipril RS (January 1, 2004)
USP Ramipril Related Compound A RS (January 1, 2004)
USP Repaglinide RS (September 1, 2003)
USP Repaglinide Related Compound A RS (September 1, 2003)
USP Repaglinide Related Compound B RS (September 1, 2003)
USP Repaglinide Related Compound C RS (September 1, 2003)
USP Sodium Starch Glycolate RS (January 1, 2004)
USP Sumatriptan RS (March 1, 2004)
USP Sumatriptan Succinate RS (March 1, 2004)
USP Sumatriptan Succinate Related Compound A RS (March 1, 2004)
USP Sumatriptan Succinate Related Compound C RS (March 1, 2004)
USP Tacrine Hydrochloride RS (January 1, 2004)
USP Taurine RS (January 1, 2004)
USP Terazosin Hydrochloride RS (March 1, 2004)
USP Terazosin Related Compound A RS (March 1, 2004)
USP Terazosin Related Compound B RS (March 1, 2004)
USP Terazosin Related Compound C RS (March 1, 2004)
USP Tiletamine Hydrochloride RS (November 1, 2003)
USP Tinidazole RS (January 1, 2004)
USP Tinidazole Related Compound A RS (January 1, 2004)
USP Thalidomide RS (January 1, 2004)
USP Tylosin RS (November 1, 2003)
USP Urea C13 RS (January 1, 2004)
USP Valsartan Related Compound A RS (March 1, 2004)
USP Valsartan Related Compound C RS (March 1, 2004)
USP Verteporfin RS (March 1, 2004)
USP Verteporfin Related Compound A RS (March 1, 2004)
USP Vinorelbin Related Compound A RS (March 1, 2004)
USP Vitexin RS (March 1, 2004)
USP Zileuton RS (January 1, 2004)
USP Zileuton Related Compound A RS (November 1, 2003)
USP Zileuton Related Compound B RS (November 1, 2003)
USP Zileuton Related Compound C RS (November 1, 2003)

The official dates of any *USP 26* or *NF 21* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

USP Alteplase RS
USP Amiloxate RS
USP Positive Bioreaction RS
USP Cefpiramide RS
USP Cinoxate RS
USP Clonazepam Related Compound C RS
USP Decoquinate RS
USP Desflurane RS
USP Dextran 40 RS
USP Dextran 70 RS
USP Diethylstilbestrol Diphosphate RS
USP Enalapril Related Compound B RS
USP Enzacamene RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS
USP Lactase RS
USP Medroxyprogesterone Acetate Related Compound A RS
USP Menotropins RS
USP Methyldopa–Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Δ^8-tetrahydrocannabinol RS
USP Δ^9-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

USP 26 MONOGRAPHS

Levothyroxine Sodium Tablets

Change to read:

Dissolution ⟨711⟩—[NOTE—All containers that are in contact with solutions containing levothyroxine sodium are to be made of glass. •Do not use paddle stirrers with synthetic coating.•5]

▲TEST 1—▲*USP26*

Medium: 0.01 N hydrochloric acid containing 0.2% sodium ■lauryl■1S *(USP26)* sulfate; 500 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Determine the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of methanol and 0.1% phosphoric acid (60:40). •Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).•5

Standard solution—Prepare a stock solution of USP Levothyroxine RS in methanol having a known concentration of about 0.1 mg per mL. Dilute this stock solution with *Dissolution Medium* to obtain a solution having a concentration similar to that expected in the *Test solution*.

Test solution—[NOTE—Prior to use, check the filters for absorptive loss of drug.] Use a filtered portion of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation is not more than 4.0%.

Procedure—Separately inject equal volumes (about 800 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved.

Tolerances—Not less than 70% *(Q)* of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 45 minutes.

▲TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

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

Time: 15 minutes.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 15 minutes.▲*USP26*

•TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4.*

Medium: 0.01 N hydrochloric acid; 500 mL for tablets labeled to contain between 25 µg and 175 µg of levothyroxine sodium; 900 mL for tablets labeled to contain 200 µg or 300 µg of levothyroxine sodium.

Apparatus 2: 75 rpm.

Time: 45 minutes.

Determine the amount of $C_{15}H_{10}I_4NNaO_4$ dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and 85% orthophosphoric acid (700:500:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a stock solution by transferring about 100 mg of USP Levothyroxine RS, accurately weighed, to a 100-mL volumetric flask. Add 80 mL of alcohol and 1 mL of 1 N hydrochloric acid, sonicate for about 2 minutes, dilute with alcohol to volume, and mix. Dilute this stock solution with a mixture of alcohol and water (1:1) to obtain a solution having a concentration of 0.01 mg of levothyroxine per mL. Dilute this intermediate solution with *Dissolution Medium* to obtain a solution having a concentration similar to that expected in the *Test solution.*

Test solution—Use a centrifuged portion of the solution under test.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.0-mm × 12.5-cm column that contains packing L7. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation is not more than 4.0%.

Procedure—Separately inject equal volumes (about 500 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the amount of $C_{15}H_{10}I_4NNaO_4$.

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{15}H_{10}I_4NNaO_4$ is dissolved in 45 minutes.•5

Triamterene Capsules

Change to read:

Dissolution ⟨711⟩—

•TEST 1—

Medium: 1% w/v of polysorbate 20 in 0.1 N acetic acid; 900 mL.

Apparatus 2: 100 rpm.

Time: 120 minutes.

Procedure—Proceed as directed for *Test 2.*

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{12}H_{11}N_7$ is dissolved in 120 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Medium: 0.1 N hydrochloric acid; 900 mL.

Apparatus 1: 100 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_{12}H_{11}N_7$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 357 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Triamterene RS in the same *Medium.*

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{12}H_{11}N_7$ is dissolved in 45 minutes.•5

Interim Revision Announcement

DIETARY SUPPLEMENTS—MONOGRAPHS

Chondroitin Sulfate Tablets

Change to read:

Labeling—Label it to indicate the species of the source from which the chondroitin used to prepare the Tablets was derived. •The label states the content of chondroitin sulfate sodium on the dried basis; the corresponding content of chondroitin sulfate sodium on the hydrous basis may also be stated.•5

Glucosamine and Chondroitin Sulfate Tablets

Change to read:

Labeling—The label indicates the types of glucosamine salts contained in the article, and the species source from which chondroitin was derived. •The label states the content of chondroitin sulfate sodium on the dried basis; the corresponding content of chondroitin sulfate sodium on the hydrous basis may also be stated.•5

GENERAL CHAPTERS

General Tests and Assays

⟨11⟩ USP REFERENCE STANDARDS

Change to read:

▲**USP Allantoin RS**—Do not dry.▲*USP26* •Keep container tightly closed.•5

Change to read:

USP Amifostine Disulfide RS [1,3-propanediamine, *N*,*N*-(dithiodi-2,1 ethanediyl)bis, tetrahydrochloride] $C_{10}H_{30}N_4S_2Cl_4$ ✧ 412.32)—Do not dry. •Keep container tightly closed. Store in a freezer.•5

Change to read:

USP Amifostine Thiol RS [ethanethiol, 2-[(3-aminopropyl)-amino]-, dihydrochloride] ($C_5H_{16}N_2SCl_2$ ✧ 207.17)—Do not dry. •Keep container tightly closed. Store in a freezer.•5

Change to read:

USP Amitraz RS—•Do not dry. Keep container tightly closed. Protect from light.•5

Change to read:

USP Betamethasone RS—•Do not dry.•5 Keep container tightly closed.

Change to read:

USP Brinzolamide RS—•Do not dry. Keep container tightly closed. Store in a freezer.•5

Change to read:

USP Brinzolamide Related Compound A RS [brinzolamide *(S)*-isomer] ($C_{12}H_{21}N_3O_5S_3$ ✧ 383.52)—Do not dry. •Keep container tightly closed. Store in a freezer.•5

Change to read:

USP Brinzolamide Related Compound B RS [desethyl brinzolamide oxalate] ($C_{10}H_{17}N_3O_5S_3 \cdot C_2H_2O_4$ ✧ 445.49)—Do not dry. •Keep container tightly closed. Store in a freezer.•5

Change to read:

USP Bupropion Hydrochloride RS—Do not dry. •Keep container tightly closed. Store in a refrigerator.•5

Change to read:

USP Butylparaben RS—•Do not dry. Keep container tightly closed.•5

Change to read:

USP Cefepime Hydrochloride RS—Do not dry before using. •Store in a cold place. Protect from light. For quantitative applications, determine the water titrimetrically at the time of use.•5

Change to read:

USP Cefotaxime Sodium RS—Do not dry. •Keep container tightly closed. Protect from light. Store in a refrigerator.•5

Change to read:

USP Choline Chloride RS—•Dry at 65° in vacuum for 4 hours before using. Keep container tightly closed. Store in a dessicator. This material is extremely hygroscopic.•5

Change to read:

USP Clomipramine Hydrochloride RS—•Do not dry. This material is hygroscopic. Keep container tightly closed.•5

Change to read:

■**USP Powdered Red Clover Extract RS**—■1S *(USP26)* •Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•5

Change to read:

USP Clozapine RS—•Dry at 105° for 4 hours before using. Keep container tightly closed.•5

Change to read:

USP Desflurane RS—•Do not dry. After opening ampul, store in a tightly closed container. Store in a refrigerator.•5

Change to read:

USP Dorzolamide Hydrochloride RS—Do not dry. •Keep container tightly closed.•5

Interim Revision Announcement

Change to read:

USP Dorzolamide Hydrochloride Related Compound A RS **[**(4*R*,6*R*)-4-(Ethylamino)-5,6-dihydro-6-methyl-4*H*-thieno-[2,3-*b*]thiopyran-2-sulfonamide-7,7-dioxide, monohydrochloride**]** ($C_{10}H_{16}N_2O_4S_3 \cdot HCl$ ✧ 360.91)—Do not dry. •Keep container tightly closed. Store in a cool room.•$_5$

Change to read:

USP Fenoldopam Related Compound A RS **[**1-Methyl-3-benzazepine-7,8-diol, 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt)**]** ($C_{17}H_{18}ClNO_3 \cdot CH_4SO_3$ ✧ 415.89)—Do not dry. •Keep container tightly closed. Protect from light. Store in a dessicator.•$_5$

Change to read:

USP Fenoldopam Related Compound B RS **[**1*H*-3-Benzazepine-7,8-diol, 2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-, methanesulfonate (salt)**]** ($C_{16}H_{16}NO_3 \cdot CH_4SO_3$ ✧ 366.42)—Do not dry. •Keep container tightly closed. Protect from light. Store in a dessicator.•$_5$

Change to read:

■**USP Formononetin RS**—■1S *(USP26)* •Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_5$

Change to read:

USP Fosphenytoin Sodium RS—Do not dry. •For quantitative application, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.•$_5$

Change to read:

▲**USP Glutamic Acid RS**—Do not dry. •Keep container tightly closed.•$_5$ Store at room temperature.▲*USP26*

Change to read:

▲**USP Hydrocodone Bitartrate Related Compound A RS**—▲*USP26* •Do not dry. Keep container tightly closed.•$_5$

Change to read:

▲**USP Isoflupredone Acetate RS**—Dry a portion at 105° for 4 hours before using.▲*USP26* •Keep container tightly closed. Protect from light.•$_5$

Add the following:

•**USP Ketamine Hydrochloride Related Compound A RS**—Do not dry. Keep container tightly closed. Protect from light. [*Caution—Protect solution from light and use immediately after preparation.*]•$_5$

Change to read:

USP Liothyronine RS—•Do not dry before using. Keep container tightly closed. Protect from light.•$_5$

Change to read:

USP Lorazepam RS—•Do not dry.•$_5$ Keep container tightly closed. Protect from light.

Change to read:

USP Meropenem RS—•Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Store in a refrigerator.•$_5$

Change to read:

USP Methenamine RS—•Do not dry.•$_5$ Keep container tightly closed.

Change to read:

USP Nabumetone RS—Do not dry. •Keep container tightly closed. Store in a cold place.•$_5$

Change to read:

USP Ondansetron Hydrochloride RS—•Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.•$_5$

Change to read:

USP Ondansetron Related Compound A RS **[**3[(Dimethylamino)methyl]-1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one**]**—•Do not dry. Keep container tightly closed. Protect from light.•$_5$

Change to read:

USP Ondansetron Related Compound C RS **[**1,2,3,9-tetrahydro-9-methyl-4*H*-carbazol-4-one**]**—•Do not dry. Keep container tightly closed. Store in a refrigerator.•$_5$

Change to read:

USP Ondansetron Related Compound D RS **[**1,2,3,9-tetrahydro-9-methyl-3-methylene-4*H*-carbazol-4-one**]**—•Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.•$_5$

Change to read:

USP Oxfendazole RS—•Do not dry. Keep container tightly closed. Protect from light.•$_5$

Change to read:

USP Paclitaxel RS—Do not dry. •Keep container tightly closed. Protect from light. Store in a refrigerator.•$_5$

Change to read:

▲**USP Paclitaxel Related Compound A RS** **[**cephalomannine**]**—Do not dry.▲*USP26* •Keep container tightly closed. Protect from light. Store in a refigerator.•$_5$

Change to read:

▲**USP Paclitaxel Related Compound B RS** **[**10-deacetyl-7-epipaclitaxel**]**—Do not dry.▲*USP26* •Keep container tightly closed. Protect from light. Store in a refrigerator.•$_5$

Change to read:

USP Perflubron RS—Do not dry. •After opening ampul, store in a tightly closed container. Protect from light.•$_5$

Change to read:

USP Phenytoin Related Compound A RS **[**Diphenylglycine**]** ($C_{14}H_{15}NO_2$ ✧ 227.26)—Do not dry. •Keep container tightly closed. Protect from light.•$_5$

Change to read:

▲**USP Ramipril RS**—Do not dry. Keep container tightly closed.▲*USP26* •Protect from light. Store in a refrigerator.•$_5$

Change to read:

▲**USP Ramipril Related Compound A RS** **[**(2*S*,3a*S*,6a*S*)-1-[(*S*)2-[[(*S*)1-(methoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-octahydrocyclopenta[*b*]pyrrole-2-carboxylic acid**]** ($C_{22}H_{30}N_2O_5$ ✧ 402.48)—Do not dry. Keep container tightly closed.▲*USP26* •Protect from light. Store in a refrigerator.•$_5$

Change to read:

USP Taurine RS—•Do not dry. Keep container tightly closed. Protect from light.•$_5$

Change to read:

USP Temazepam RS—•Do not dry. Keep container tightly closed.•$_5$

Change to read:

USP Thalidomide RS—Dry portion in vacuum at 60° for 2 hours before using. •Keep container tightly closed. Protect from light.•$_5$

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Change to read:
USP Tiletamine Hydrochloride RS—•Dry at 105° for 4 hours before using. Keep container tightly closed.•5

Change to read:
USP Vinorelbine Related Compound A RS [4-*O*-deacetylvinorelbine**]** ($C_{43}H_{52}N_4O_7 \cdot 2C_4H_6O_6$ ✧ 1037.07—Do not dry. •Keep under inert gas with container tightly closed. Protect from light. Store in a freezer.•5

Change to read:
■**USP Vinorelbine Tartrate RS**—Do not dry.■1S (*USP26*) •Keep under inert gas with container tightly closed. Protect from light. Store in a freezer.•5

⟨724⟩ DRUG RELEASE

Change to read:

EXTENDED-RELEASE ARTICLES—GENERAL DRUG RELEASE STANDARD

Apparatus 1 and Apparatus 2

Apparatus—Proceed as directed under *Dissolution* ⟨711⟩.

Apparatus Suitability Test, Dissolution Medium, and Procedure—Proceed as directed under *Dissolution* ⟨711⟩.

Time—The test-time points, generally three, are expressed in hours. Specimens are to be withdrawn within a tolerance of ±2% of the stated time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 1*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range.

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units ($L_1 + L_2$) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.
L_3	12	The average value of the 24 units ($L_1 + L_2 + L_3$) lies within each of the stated ranges, and is not less than the stated amount at the final test time; not more than 2 of the 24 units are more than 10% of labeled content outside each of the stated ranges; not more than 2 of the 24 units are more than 10% of labeled content below the stated amount at the final test time; and none of the units is more than 20% of labeled content outside each of the stated ranges or more than 20% of labeled content below the stated amount at the final test time.

Apparatus 3 (Reciprocating Cylinder)

Apparatus—The assembly consists of a set of cylindrical, flat-bottomed glass vessels; a set of glass reciprocating cylinders; stainless steel fittings (type 316 or equivalent) and screens that are made of suitable nonsorbing and nonreactive material and that are designed to fit the tops and bottoms of the reciprocating cylinders; and a motor and drive assembly to reciprocate the cylinders vertically inside the vessels and, if desired, index the reciprocating cylinders horizontally to a different row of vessels. The vessels are partially immersed in a suitable water bath of any convenient size that permits holding the temperature at 37 ± 0.5° during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating cylinder. A device is used that allows the reciprocation rate to be selected and maintained at the dip rate specified in the individual monograph, within ± 5%. An apparatus that permits observation of the specimens and reciprocating cylinders is preferable. The components conform to the dimensions shown in *Figure 1* unless otherwise specified in the individual monograph.

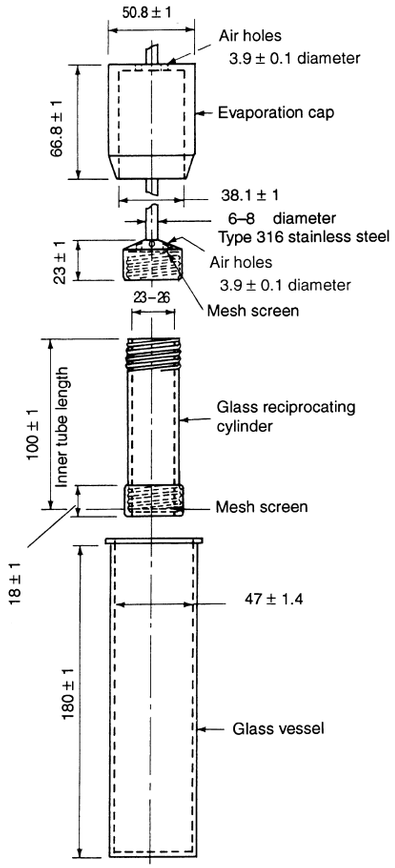

Fig. 1. Apparatus 3.
(All measurements are expressed in mm unless noted otherwise.)

USP Reference Standards ⟨11⟩—USP Chlorpheniramine Extended-Release Tablets RS *(Drug Release Calibrator, Single Unit).*

Apparatus Suitability Test—Individually test 1 tablet of the USP Drug Release Calibrator Tablets (Single Unit) according to the operation conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in each vessel of the apparatus, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 dosage-form unit in each of the six reciprocating cylinders, taking care to exclude air bubbles from the surface of each dosage-form unit, and immediately operate the apparatus as specified in the individual monograph. During the upward and downward stroke, the reciprocating cylinder moves through a total distance of 9.9 to 10.1 cm. Within the time interval specified, or at each of the times stated, raise the reciprocating cylinders and withdraw a portion of the solution under test from a zone midway between the surface of the *Dissolution Medium* and the bottom of each vessel. Perform the analysis as directed in the individual monograph. If necessary, repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not fewer than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium.* Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Time and Interpretation—Proceed as directed under *Apparatus 1 and 2.*

Apparatus 4 (Flow-Through Cell)

Apparatus—The assembly consists of a reservoir and a pump for the *Dissolution Medium;* a flow-through cell; a water bath that maintains the *Dissolution Medium* at 37 ± 0.5° (see *Figures 2* and *3*). The cell size is specified in the individual monograph.

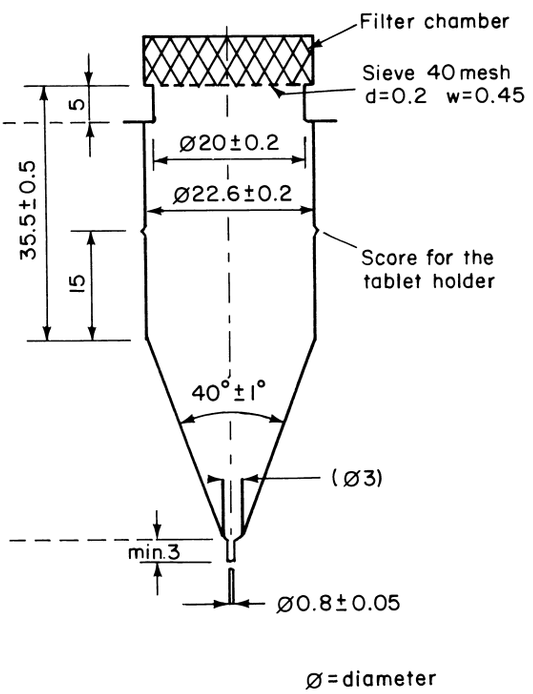

Fig. 2. Large cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

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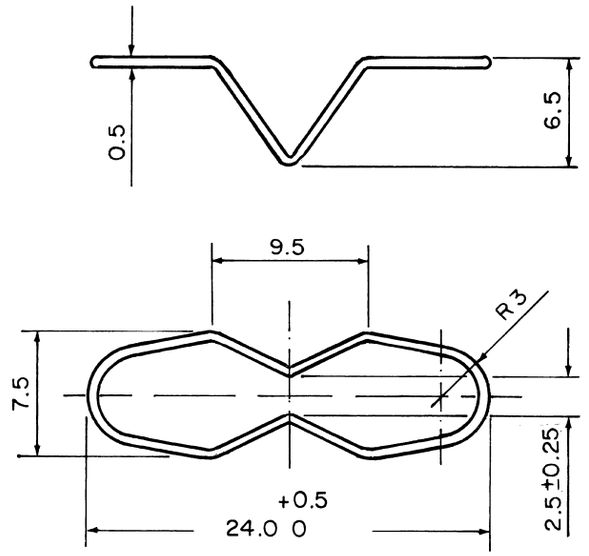

Fig. 2a. Tablet holder for the large cell.
(All measurements are expressed in mm unless noted otherwise.)

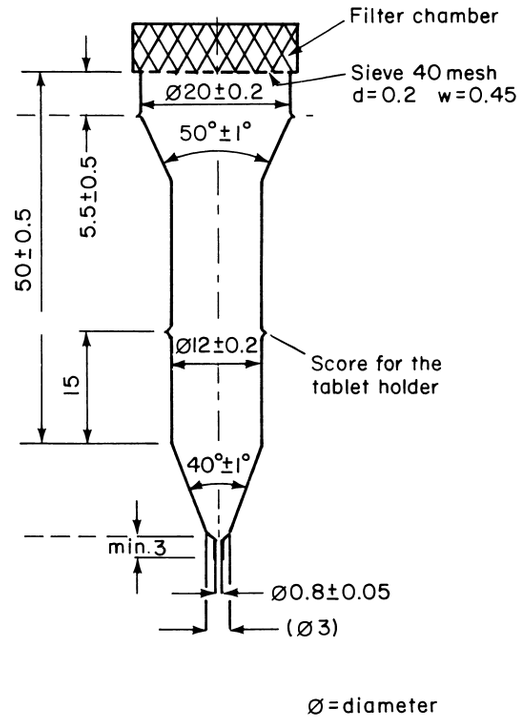

Fig. 3. Small cell for tablets and capsules.
(All measurements are expressed in mm unless noted otherwise.)

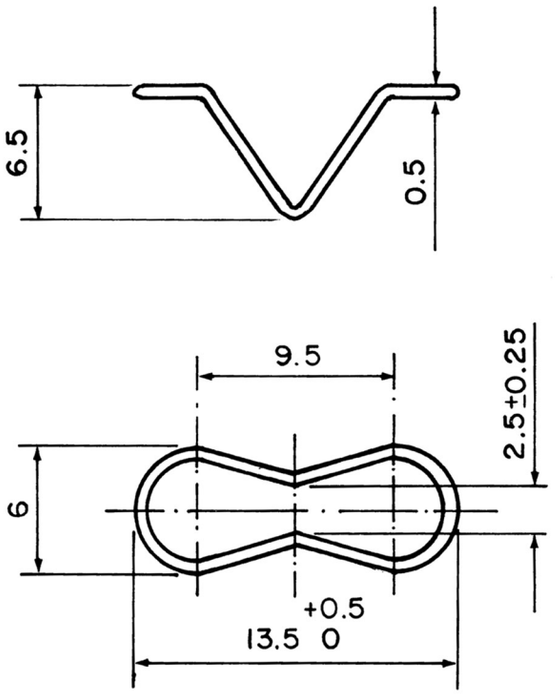

Fig. 3a. Tablet holder for the small cell.
(All measurements are expressed in mm unless noted otherwise.)

The pump forces the *Dissolution Medium* upwards through the flow-through cell. The pump has a delivery range between 240 and 960 mL per hour, with standard flow rates of 4, 8, and 16 mL per minute. It must be volumetric to deliver constant flow independent of flow resistance in the filter device; the flow profile is sinusoidal with a pulsation of 120 ± 10 pulses per minute.

The flow-through cell (see *Figures 2* and *3*), of transparent and inert material, is mounted vertically with a filter system (specified in the individual monograph) that prevents escape of undissolved particles from the top of the cell; standard cell diameters are 12 and 22.6 mm; the bottom cone is usually filled with small glass beads of about 1-mm diameter with one bead of about 5 mm positioned at the apex to protect the fluid entry tube; a tablet holder (see *Figures 2a* and *3a*) is available for positioning of special dosage forms, for example, inlay tablets. The cell is immersed in a water bath, and the temperature is maintained at 37 ± 0.5°.

The apparatus uses a clamp mechanism and two O-rings for the fixation of the cell assembly. The pump is separated from the dissolution unit in order to shield the latter against any vibrations originating from the pump. The position of the pump should not be on a level higher than the reservoir flasks. Tube connections are as short as possible. Use polytef tubing with a 1.6-mm inner diameter and chemically inert flanged-end connections.

Apparatus Suitability Test and Dissolution Medium—Proceed as directed under *Dissolution* ⟨711⟩.

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Procedure—Place the glass beads into the cell specified in the monograph. Place 1 dosage-form unit on top of the beads or, if specified in the monograph, on a wire carrier. Assemble the filter head and fix the parts together by means of a suitable clamping device. Introduce by the pump the *Dissolution Medium* warmed to 37 ± 0.5° through the bottom of the cell to obtain the flow rate specified in the individual monograph and measured with an accuracy of 5%. Collect the eluate by fractions at each of the times stated. Perform the analysis as directed in the individual monograph. Repeat the test with additional dosage-form units.

Where capsule shells interfere with the analysis, remove the contents of not fewer than 6 capsules as completely as possible, and dissolve the empty capsule shells in the specified volume of *Dissolution Medium.* Perform the analysis as directed in the individual monograph. Make any necessary correction. Correction factors greater than 25% of the labeled content are unacceptable.

Time and Interpretation—Proceed as directed under *Apparatus 1 and 2.*

Change to read:

TRANSDERMAL DELIVERY SYSTEMS—GENERAL DRUG RELEASE STANDARDS

Apparatus 5 (Paddle over Disk)

Apparatus—Use the paddle and vessel assembly from *Apparatus 2* as described under *Dissolution* ⟨711⟩, with the addition of a stainless steel disk assembly[1] designed for holding the transdermal system at the bottom of the vessel. Other appropriate devices may be used, provided they do not sorb, react with, or interfere with the specimen being tested[2]. The temperature is maintained at 32 ± 0.5°. A distance of 25 ± 2 mm between the paddle blade and the surface of the disk assembly is maintained during the test. The vessel may be covered during the test to minimize evaporation. The disk assembly for holding the transdermal system is designed to minimize any "dead" volume between the disk assembly and the bottom of the vessel. The disk assembly holds the system flat and is positioned such that the release surface is parallel with the bottom of the paddle blade (see *Figure 4*).

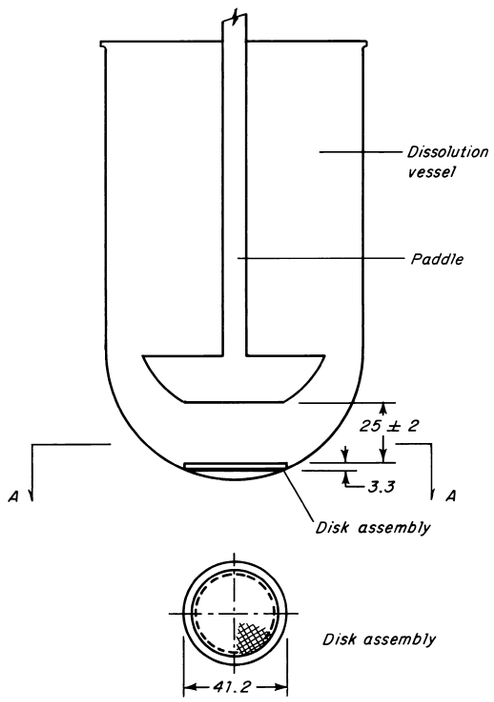

Fig. 4. Paddle Over Disk.
(All measurements are expressed in mm unless noted otherwise.)

Apparatus Suitability Test and Dissolution Medium—Proceed as directed for *Apparatus 2* under *Dissolution* ⟨711⟩.

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel, assemble the apparatus without the disk assembly, and equilibrate the medium to 32 ± 0.5°. Apply the transdermal system to the disk assembly, assuring that the release surface of the system is as flat as possible. The system may be attached to the disk by applying a suitable adhesive[3] to the disk assembly. Dry for 1 minute. Press the system, release surface side up, onto the adhesive-coated side of the disk assembly. If a membrane[4] is used to support the system, it is applied so that no air bubbles occur between the membrane and the release surface. Place the disk assembly flat at the bottom of the vessel with the release surface facing up

[1] Disk assembly (stainless support disk) may be obtained from Millipore Corp., Ashley Rd., Bedford, MA 01730.

[2] A suitable device is the watchglass-patch-polytef mesh sandwich assembly available as the Transdermal Sandwich™ from Hanson Research Corp., 9810 Variel Ave., Chatsworth, CA 91311.

Change to read:

[3] Use Dow Corning, •MD7-4502 Silicone Adhesive 65% in ethyl acetate,•5 or the equivalent.

[4] Use Cuprophan, Type 150 pm, 11 ± 0.5-µm thick, an inert, porous cellulosic material, which is available from Medicell International Ltd., 239 Liverpool Road, London NI ILX, England.

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and parallel to the edge of the paddle blade and surface of the *Dissolution Medium.* The bottom edge of the paddle is 25 ± 2 mm from the surface of the disk assembly. Immediately operate the apparatus at the rate specified in the monograph. At each sampling time interval, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the blade, not less than 1 cm from the vessel wall. Perform the analysis on each sampled aliquot as directed in the individual monograph, correcting for any volume losses, as necessary. Repeat the test with additional transdermal systems.

Time—The test time points, generally three, are expressed in hours. Specimens are to be withdrawn within a tolerance of ±15 minutes or ±2% of the stated time, the tolerance that results in the narrowest time interval being selected.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 4* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

Acceptance Table 4

Level	Number Tested	Criteria
L_1	6	No individual value lies outside the stated range.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within the stated range. No individual value is outside the stated range by more than 10% of the average of the stated range.
L_3	12	The average value of the 24 units (L_1 + L_2 + L_3) lies within the stated range. Not more than 2 of the 24 units are outside the stated range by more than 10% of the average of the stated range; and none of the units is outside the stated range by more than 20% of the average of the stated range.

Apparatus 6 (Cylinder)

Apparatus—Use the vessel assembly from *Apparatus 1* as described under *Dissolution* ⟨711⟩, except to replace the basket and shaft with a stainless steel cylinder stirring element and to maintain the temperature at 32 ± 0.5° during the test. The shaft and cylinder components of the stirring element are fabricated of stainless steel to the specifications shown in *Figure 5*. The dosage unit is placed on the cylinder at the beginning of each test. The distance between the inside bottom of the vessel and the cylinder is maintained at 25 ± 2 mm during the test.

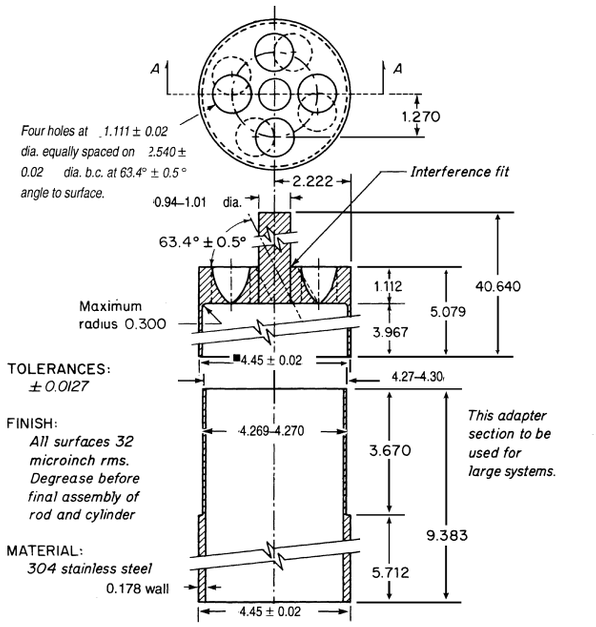

Fig. 5. Cylinder Stirring Element.[5]
(All measurements are expressed in cm unless noted otherwise.)

Dissolution Medium—Use the medium specified in the individual monograph (see *Dissolution* ⟨711⟩).

Procedure—Place the stated volume of the *Dissolution Medium* in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, and equilibrate the *Dissolution Medium* to 32 ± 0.5°. Unless otherwise directed in the individual monograph, prepare the test system prior to the test as follows. Remove the protective liner from the system, and place the adhesive side on a piece of Cuprophan[4] that is not less than 1 cm larger on all sides than the system. Place the system, Cuprophan covered side down, on a clean surface, and apply a suitable adhesive[3] to the exposed Cuprophan borders. If necessary, apply additional adhesive to the back of the system. Dry for 1 minute. Carefully apply the adhesive-coated side of the system to the exterior of the cylinder such that the long axis of the system fits around the circumference of the cylinder. Press the Cuprophan covering to remove trapped air bubbles. Place the cylinder in the apparatus, and immediately rotate at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a quantity of *Dissolution Medium* for analysis from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating cylinder, not less than 1 cm from the vessel wall. Perform the analysis as directed in the individual monograph, correcting for any volume losses as necessary. Repeat the test with additional transdermal drug delivery systems.

Time—Proceed as directed under *Apparatus 5.*

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient released from the system conform to *Acceptance Table 4* for transdermal drug delivery systems. Continue testing through the three levels unless the results conform at either L_1 or L_2.

[5] The cylinder stirring element is available from Accurate Tool, Inc., 25 Diaz St., Stamford, CT 06907, or from VanKel Technology Group, 13000 Weston Parkway, Cary, NC 27513.

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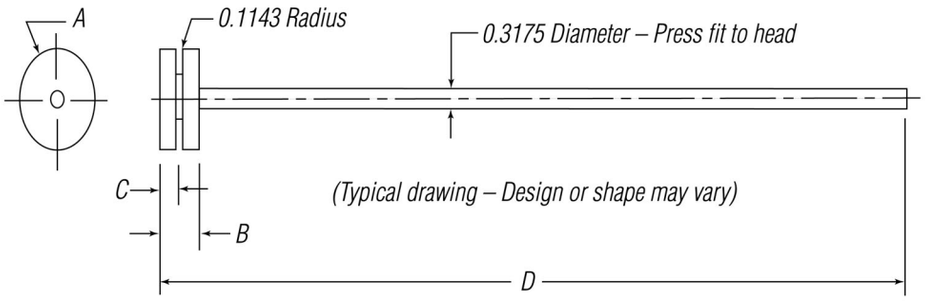
Apparatus 7 (Reciprocating Holder)

NOTE—This apparatus may also be specified for use with a variety of dosage forms.

Apparatus—The assembly consists of a set of volumetrically calibrated or tared solution containers made of glass or other suitable inert material[6], a motor and drive assembly to reciprocate the system vertically and to index the system horizontally to a different row of vessels automatically if desired, and a set of suitable sample holders (see *Figure 6* and *Figures 7a–7d*). The solution containers are partially immersed in a suitable water bath of any convenient size that permits maintaining the temperature, *T,* inside the containers at 32 ± 0.5° or within the allowable range, as specified in the individual monograph, during the test. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smooth, vertically reciprocating sample holder. Apparatus that permits observation of the system and holder during the test is preferable. Use the size container and sample holder as specified in the individual monograph.



Dimensions are in centimeters

	HEAD				ROD		O-RING
System[a]	*A (Diameter)*	*B*	*C*	Material[b]	*D*	Material[c]	*(not shown)*
1.6cm^2	1.428	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-113-V884-75
2.5cm^2	1.778	0.9525	0.4750	SS/VT	30.48	SS/P	Parker 2-016-V884-75
5cm^2	2.6924	0.7620	0.3810	SS/VT	8.890	SS/P	Parker 2-022-V884-75
7cm^2	3.1750	0.7620	0.3810	SS/VT	30.48	SS/P	Parker 2-124-V884-75
10cm^2	5.0292	0.6350	0.3505	SS/VT	31.01	SS/P	Parker 2-225-V884-75

[a] Typical system sizes.
[b] SS/VT=Either stainless steel or virgin Teflon.
[c] SS/P=Either stainless steel or Plexiglas.

Fig. 6. Reciprocating Disk Sample Holder.[7]

[6] The materials should not sorb, react with, or interfere with the specimen being tested.

[7] The reciprocating disk sample holder may be purchased from ALZA Corp., 1900 Charleston Road, P.O. Box 7210, Mt. View, CA 94039–7210 or VanKel Technology Group.

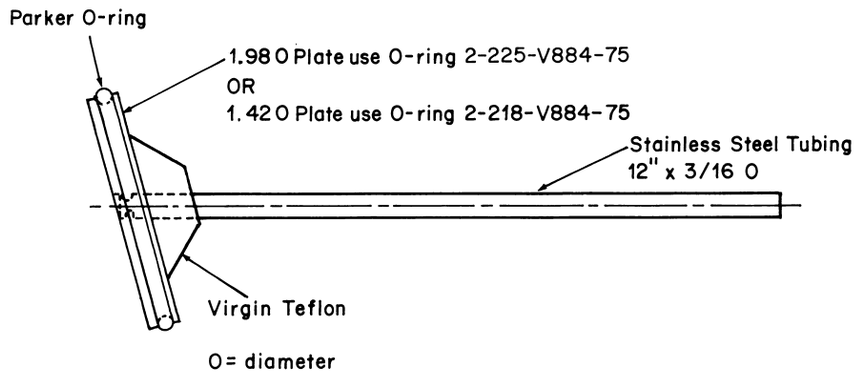


Fig. 7a. Transdermal system holder—angled disk.

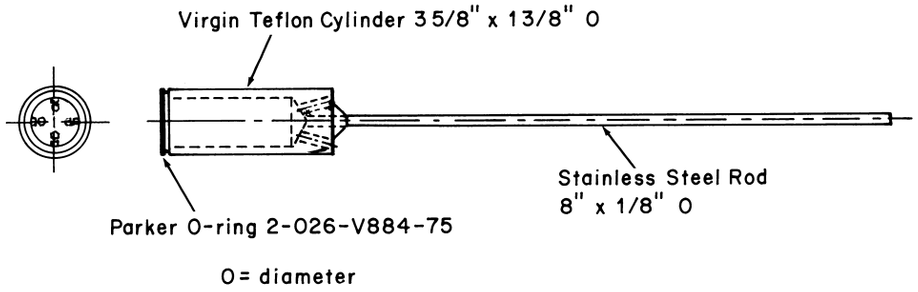


Fig. 7b. Transdermal system holder—cylinder.

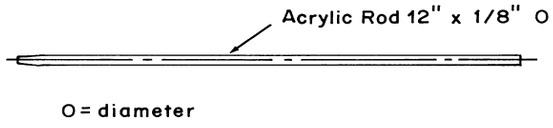
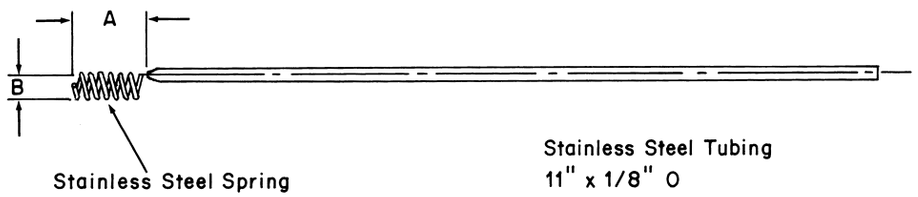


Fig. 7c. Oral extended-release tablet holder—rod, pointed for gluing.



Stainless Steel Spring Dimensions

A	B
1.45	.58 O
1.40	.31 O
.96	.33 O
.60	.25 O

O = diameter

Fig. 7d. Oral extended-release tablet holder—spring holder.

Dissolution Medium—Use the *Dissolution Medium* specified in the individual monograph (see *Dissolution* ⟨711⟩).

Sample Preparation A (Coated tablet drug delivery system)—Attach each system to be tested to a suitable sample holder (e.g., by gluing system edge with 2-cyano acrylate glue onto the end of a plastic rod or by placing the system into a small nylon net bag at the end of a plastic rod or within a metal coil attached to a metal rod).

Sample Preparation B (Transdermal drug delivery system)—Press the system onto a dry, unused piece of Cuprophan[4], nylon netting, or equivalent with the adhesive side against the selected substrate, taking care to eliminate air bubbles between the substrate and the release surface. Attach the system to a suitable sized sample holder with a suitable O-ring such that the back of the system is adjacent to and centered on the bottom of the disk-shaped sample holder or centered around the circumference of the cylindrical-shaped sample holder. Trim the excess substrate with a sharp blade.

Sample Preparation C (Other drug delivery systems)—Attach each system to be tested to a suitable holder as described in the individual monograph.

Procedure—Suspend each sample holder from a vertically reciprocating shaker such that each system is continuously immersed in an accurately measured volume of *Dissolution Medium* within a calibrated container pre-equilibrated to temperature, *T.* Reciprocate at a frequency of about 30 cycles per minute with an amplitude of about 2 cm, or as specified in the individual monograph, for the specified time in the medium specified for each time point. Remove the solution containers from the bath, cool to room temperature, and add sufficient solution (i.e., water in most cases) to correct for evaporative losses. Perform the analysis as directed in the individual monograph. Repeat the test with additional drug delivery systems as required in the individual monograph.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of the active ingredients released from the system conform to *Acceptance Table 1* for coated tablet drug delivery systems, to *Acceptance Table 4* for transdermal drug delivery systems, or as specified in the individual monograph. Continue testing through the three levels unless the results conform at either L_1 or L_2.

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ERRATA

Following is a list of errata and corrections to *USP 26–NF 21*. The page number indicates where the item is found in *USP 26–NF 21*. If necessary, this list will be updated with every issue of *PF*. This information will also be available as a cumulative table in the next available *Supplement* and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement. USP staff are available to respond to questions regarding the accuracy of a particular requirement by calling 1-800-822-USPC.

Page	Title	Section	Description
369	*Cefotaxime Sodium*	*Assay*	Line 10 under *Chromatographic system*: Change "per minute until the proportion of *Solution A* is 100%," to: per minute until the proportion of *Solution B* is 100%,
666	*Doxycycline*	*Assay*	Line 6 under *Procedure*: Change "100(CP/W)(r_U/r_S)," to: 50(CP/W)(r_U/r_S),
877	*Griseofulvin Tablets*	*Assay*	Line 4 under *Procedure*: Change "(r_U/r_S)," to: $PC(r_U/r_S)$,
983	*Iobenguane I 123 Injection*	*Assay for iobenguane sulfate*	Lines 2–3 under *Chromatographic system*: Change "a 4.6-mm × 250-cm column" to: a 4.6-mm × 25-cm column
1485	*Piperacillin for Injection*	*Related compounds*	Line 6 under *Procedure*: Change "$0.1C(P/A)(RRF_i)(r_i/rSp)$," to: $0.1C(P/A)(RRF_i)(r_i/r_{Sp})$,
1519	*Povidone*	*Limit of aldehydes*	Line 3 under *Procedure*: Change "Add 2.5 mL of *Phosphate* and" to: Add 2.5 mL of *Phosphate buffer* and
1715	*Strontium Chloride Sr 89 Injection*	*Chemical purity (Limit of aluminum)*	Line 1 under *Standard preparations*: Change "Transfer 2000 g of aluminum metal" to: Transfer 2000 mg of aluminum metal
		Assay	Line 2 under *Strontium stock solution:* Change "1000-mL volumetric flask" to: 100-mL volumetric flask
2458	*Reagents*	*Reagent Specifications*	Page 2490: Change "D-d-4-Hydroxyphenylglycine" to: D-α-4-Hydroxyphenylglycine
2545	*Reference Tables*	*Containers for Dispensing Capsules and Tablets*	Remove *Valerian Capsules*, as the monograph has not yet become official.
		Solubilities	Benzocaine, seventh column: Change "almond oil or olive oil, 0-50" to: almond oil or olive oil, 30-50; *Footnote 1:* Change "i.e., 1 mL dissolved in mL of solvent." to: i.e., 1 mL dissolved in _____ mL of solvent.
2775	*Low-Substituted Hydroxypropyl Cellulose*	*Assay*	Lines 2 and 3: Change "Hydroxypropyl Methylcellulose" to: Hypromellose
2776	*Hydroxypropyl Methylcellulose*	*cross reference*	Change "see Hydroxypropyl Methylcellulose USP" to: see Hypromellose USP
First Supplement			
2961	*Felodipine Extended-Release Tablets*	*Figure 1*	*Apparatus C*: Change the length measurement "10.0 mm" to: 40.0 mm
Second Supplement			
3128	*Tiamulin Fumarate*	*Content of fumarate*	Line 6-7: Change "Each mL of 0.1 N sodium hydroxide is equivalent to 0.58 mg of fumarate:" to: Each mL of 0.1 N sodium hydroxide is equivalent to 5.8 mg of fumarate:

Interim Revision Announcement

IN-PROCESS REVISION

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

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

BRIEFING

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

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

•new text•

if slated for an *Interim Revision Announcement to USP 26–NF 21* (*IRA*), thus:

▲new text▲*USP27*

if slated for *USP 27–NF 22*, and thus:

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, and ■2S (*USP 27*) indicates that the proposed revision is slated for the *Second Supplement to USP 27*, and ▲*USP27* and ▲*NF22* indicate that the revisions are proposed for *USP 27* and *NF 22*, respectively.

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

In-Process Revision

MONOGRAPHS (USP)

BRIEFING

Alprostadil, *USP 26* page 67 and page 2941 of the *First Supplement;* **Carboprost Tromethamine,** *USP 26* page 339; **Cortisone Acetate,** *USP 26* page 517; **Desoxycorticosterone Acetate,** *USP 26* page 556; **Dexamethasone Acetate,** *USP 26* page 562; **Diethylstilbestrol,** *USP 26* page 604; **Ergonovine Maleate,** *USP 26* page 721; **Estradiol,** *USP 26* page 742; **Conjugated Estrogens,** *USP 26* page 747; **Estrone,** *USP 26* page 750; **Hydrocortisone,** *USP 26* page 913 and page 2969 of the *First Supplement;* **Hydroxyprogesterone Caproate,** *USP 26* page 933; **Medroxyprogesterone Acetate,** *USP 26* page 1139 and page 2974 of the *First Supplement;* **Methylergonovine Maleate,** *USP 26* page 1206; **Methylprednisolone Acetate,** *USP 26* page 1211; **Nandrolone Decanoate,** *USP 26* page 1269; **Prednisolone Acetate,** *USP 26* page 1529; **Progesterone,** *USP 26* page 1554; **Ritodrine Hydrochloride,** *USP 26* page 1652; **Testosterone,** *USP 26* page 1781; **Triamcinolone Acetonide,** *USP 26* page 1864. Revisions are proposed to establish consistency with the system of labeling established in 1993 by the USP Drug Nomenclature Committee (page 5618 of *PF* 19(4)[July–Aug. 1993]). Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms, a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that, where the label states that it is sterile, it must meet the requirements of the test for *Sterility* ⟨71⟩ and of the test for *Bacterial endotoxins* ⟨85⟩. In addition, where the label states that it must be subjected to further processing during the preparation of injectable dosage forms, it must meet the requirements of the test for *Bacterial endotoxins* ⟨85⟩. In some of the monographs it is also proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA1: C. Anthony) RTS—40156-1

In-Process Revision

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Alprostadil RS.*

■*USP Endotoxin RS.*■2S (*USP27*)
USP Prostaglandin A_1 RS. ■*USP Prostaglandin B_1 RS.*■*USP26*

Change to read:

Limit of foreign prostaglandins—

▲TEST 1—

NOTES—Use freshly prepared solutions. Measure the peak responses at the following wavelengths: prostaglandin A_1 at 224 nm; prostaglandin B_1 at 280 nm; and all other foreign prostaglandin impurities at 200 nm.

Mobile phase—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Alprostadil RS, USP Prostaglandin A_1 RS, and USP Prostaglandin B_1 RS in a mixture of methanol and water (9:1), and dilute quantitatively, and stepwise if necessary, with a mixture of methanol and water (9:1) to obtain a solution having known concentrations of about 6 µg per mL, 15 µg per mL, and 6 µg per mL, respectively.

Test solution—Dissolve about 15 mg of Alprostadil, accurately weighed, in 5 mL of a mixture of methanol and water (9:1), and mix.

Chromatographic system—Proceed as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution between prostaglandin A_1 and alprostadil is not less than 7.5, and the relative standard deviation from the peaks at their respective wavelength for replicated injections is not more than 4.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses at 200 nm, 224 nm, and 280 nm. Calculate the percentage of prostaglandin A_1 and prostaglandin B_1 in the portion of Alprostadil taken by the formula:

$$500(C_S / W)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Prostaglandin A_1 RS or USP Prostaglandin B_1 RS in the *Standard solution; W* is the weight, in mg, of Alprostadil taken for the *Test solution; r_i* is the peak response for prostaglandin A_1 or prostaglandin B_1 obtained from the *Test solution;* and r_S is the peak response of prostaglandin A_1 or prostaglandin B_1 obtained from the *Standard solution:* not more than 1.5% of prostaglandin A_1 is found; and not more than 0.1% of prostaglandin B_1 is found. Calculate the percentage of each impurity occurring at 200 nm and eluting before prostaglandin A_1 in the portion of Alprostadil taken by the formula:

$$500(C_S / W)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Alprostadil RS in the *Standard solution; r_i* is the peak response for each impurity obtained from the *Test solution; r_S* is the peak response for alprostadil obtained from the *Standard solution;* and the other terms are as defined herein: not more than 0.9% of any foreign prostaglandin impurity is found. Calculate the percentage of any impurity having a relative retention time of 0.6, relative to the prostaglandin A_1 peak detected at 224 nm, in the portion of Alprostadil taken by the formula:

$$500(C_S / W)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Prostaglandin A_1 RS in the *Standard solution; r_i* is the peak response for any impurity having a relative retention time of 0.6, relative to the prostaglandin A_1 peak, obtained from the *Test solution; r_S* is the peak response of prostaglandin A_1 obtained from the *Standard solution;* and the other terms are as defined herein: not more than 0.9% of any impurity having a relative retention time of 0.6, relative to the prostaglandin A_1 peak, is found.

TEST 2—

Mobile phase—Prepare a filtered and degassed mixture of methanol, acetonitrile, and 0.02 M monobasic potassium phosphate (2:1:1), and adjust with phosphoric acid to a pH of 3. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Alprostadil RS in a mixture of acetonitrile and water (1:1) to obtain a solution having a known concentration of about 10 µg per mL.

Test solution—Dissolve about 25 mg of Alprostadil, accurately weighed, in 5 mL of a mixture of acetonitrile and water (1:1), using ultrasound if necessary.

Identification solution—Use the *Standard solution* under *Test 1.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a photodiode array detector or equivalent capable of detecting UV wavelengths between 200 nm and 300 nm and a 4.6-mm x 25-cm column that contains packing L1. The flow rate is about 1.2 mL per minute. Chromatograph the *Identification solution* as directed for *Procedure:* the relative retention times for prostaglandin A_1 and alprostadil are about 1.2 and 1.0, respectively; the resolution between prostaglandin A_1 and alprostadil is not less that 4.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation determined from the main peak for replicated injections is not ~~less~~

▲more▲*USP27*
than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses at 200 nm, 224 nm, and 280 nm. Calculate the percentage of each impurity occurring at 200 nm and eluting after prostaglandin A_1, excluding prostaglandin B_1, in the portion of Alprostadil taken by the formula:

$$500(C_S / W)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Alprostadil RS in the *Standard solution; W* is the weight, in mg, of Alprostadil taken for the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for alprostadil obtained from the *Standard solution:* the sum of the peaks having relative retention times of 2.0 and 2.3 is not more than 0.6%; not more than 0.9% of any other foreign prostaglandin impurity is found; and not more than 2.0% of total impurities is found, the results for *Test 1* and *Test 2* being added.▲*USP26*

Add the following:

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

BRIEFING

Amifostine, *USP 26* page 110; **Aminocaproic Acid,** *USP 26* page 119; **Atenolol,** *USP 26* page 185; **Bretylium Tosylate,** *USP 26* page 263; **Bumetanide,** *USP 26* page 274; **Chlorothiazide,** *USP 26* page 425; **Deslanoside,** *USP 26* page 553; **Diazoxide,** *USP 26* page 590; **Dipyridamole,** *USP 26* page 644; **Dobutamine Hydrochloride,** *USP 26* page 651; **Dopamine Hydrochloride,** *USP 26* page 659; **Ethacrynic Acid,** *USP 26* page 754; **Fenoldopam Mesylate,** *USP 26* page 776 and page 2964 of the *First Supplement;* **Furosemide,** *USP 26* page 837; **Hydralazine Hydrochloride,** *USP 26* page 907; **Inamrinone,** *USP 26* page 958; **Labetalol Hydrochloride,** *USP 26* page 1051; **Menadiol Sodium Diphosphate,** *USP 26* page 1145; **Menadione,** *USP 26* page 1146; **Metaraminol Bitartrate,** *USP 26* page 1173; **Methyldopate Hydrochloride,** *USP 26* page 1203; **Methylene Blue,** *USP 26* page 1205; **Metoprolol Tartrate,** *USP 26* page 1222; **Diluted Nitroglycerin,** *USP 26* page 1319; **Norepinephrine Bitartrate,** *USP 26* page 1327; **Papaverine Hydrochloride,** *USP 26* page 1395; **Phentolamine Mesylate,** *USP 26* page 1455; **Procainamide Hydrochloride,** *USP 26* page 1543; **Propranolol Hydrochloride,** *USP 26* page 1577; **Quinidine Gluconate,** *USP 26* page 1605; **Reserpine,** *USP 26* page 1625; **Sodium Nitrite,** *USP 26* page 1700; **Sodium Nitroprusside,** *USP 26* page 1700; **Tolazoline Hydrochloride,** *USP 26* page 1852; **Urea,** *USP 26* page 1912; **Verapamil Hydrochloride,** *USP 26* page 1924. It is proposed to revise these monographs to establish consistency with the system of labeling established in 1993 by the USP Drug Nomenclature Committee (see page 5618 of *PF* 19(4) [July-Aug. 1993]). Specifically, for drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms, it is proposed to include a *Labeling* statement to indicate that the drug substance is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed to specify that where the label states that it is sterile, it must meet the requirements under *Sterility Tests* ⟨71⟩ and *Bacterial Endotoxins Test* ⟨85⟩. In addition, where the label states that it must be subjected to further processing during the preparation of injectable dosage forms, it must meet the requirements under *Bacterial Endotoxins Test* ⟨85⟩. Also, in several of these monographs, it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA5: A. Wilk) RTS—40124-1

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Amifostine RS. USP Amifostine Thiol RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

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Add the following:

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

BRIEFING

Aminocaproic Acid, *USP 26* page 119—See briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-2

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Aminocaproic Acid RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Aminopentamide Sulfate, *USP 26* page 123. For clarification, it is proposed to specify the solvent for the preparation of the 0.1 N lithium methoxide VS in the *Assay.* However, as it is USP's policy to replace methods that use benzene, interested parties are encouraged to submit validated alternative procedures for review and possible adoption by the Expert Committee on Veterinary Drugs.

(VET: I. DeVeau) RTS—39973-1

Change to read:

Assay—Dissolve about 500 mg of Aminopentamide Sulfate, accurately weighed, in 100 mL of dimethylformamide in a suitable container. Add 5 drops of thymol blue TS, and titrate with 0.1 N lithium methoxide VS

■in benzene■2S (*USP27*)
to a deep blue endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N lithium methoxide is equivalent to 19.72 mg of $C_{19}H_{24}N_2O \cdot H_2SO_4$.

BRIEFING

Aminophylline, *USP 26* page 124; **Brompheniramine Maleate,** *USP 26* page 270; **Bupivacaine Hydrochloride,** *USP 26* page 276; **Calcium Chloride,** *USP 26* page 305; **Chloroprocaine Hydrochloride,** *USP 26* page 422; **Chlorpheniramine Maleate,** *USP 26* page 427; **Chromic Chloride,** *USP 26* page 447; **Dextrose**, *USP 26* page 581; **Dibucaine Hydrochloride,** *USP 26* page 593; **Diphenhydramine Hydrochloride,** *USP 26* page 637; **Dyphylline,** *USP 26* page 677; **Ephedrine Sulfate,** *USP 26* page 706; **Epinephrine,** *USP 26* page 709; **Fructose,** *USP 26* page 834; **Gallamine Triethiodide,** *USP 26* page 846; **Isoproterenol Hydrochloride,** *USP 26* page 1029; **Lidocaine Hydrochloride,** *USP 26* page 1078; **Manganese Chloride,** *USP 26* page 1123; **Mepivacaine Hydrochloride,** *USP 26* page 1154; **Methohexital,** *USP 26* page 1188; **Potassium Chloride,** *USP 26* page 1502; **Prilocaine Hydrochloride,** *USP 26* page 1536; **Procaine Hydrochloride,** *USP 26* page 1547; **Promazine Hydrochloride,** *USP 26* page 1558; **Promethazine Hydrochloride,** *USP 26* page 1560; **Propoxycaine Hydrochloride,** *USP 26* page 1566; **Sodium Acetate,** *USP 26* page 1686; **Succinylcholine Chloride,** *USP 26*

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page 1716; **Terbutaline Sulfate,** *USP 26* page 1774 and page 2998 of the *First Supplement;* **Tetracaine Hydrochloride,** *USP 26* page 1787; **Theophylline,** *USP 26* page 1801; **Thiopental Sodium,** *USP 26* page 1822. Revisions are proposed to establish consistency with the system of *Labeling* established in 1993 by the USP Drug Nomenclature Committee, as published on page 5618 of *PF* 19(4) [July–Aug. 1993]. Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms, a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that where the label states that it is sterile it must meet the requirements for *Sterility* ⟨71⟩ and *Bacterial endotoxins* ⟨85⟩. In addition where the label states that it must be subjected to further processing during the preparation of injectable dosage forms it must meet the requirements for *Bacterial endotoxins* ⟨85⟩. In some monographs it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA1: K. Russo) RTS—40176-1

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

USP Reference standards ⟨11⟩*—USP Theophylline RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Change to read:

Labeling—Label it to indicate whether it is anhydrous or hydrous and also to state the content of anhydrous theophylline.

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

Add the following:

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

BRIEFING

Ammonium Chloride, *USP 26* page 134; **Ammonium Molybdate,** *USP 26* page 135; **Cimetidine,** *USP 26* page 453; **Deferoxamine Mesylate,** *USP 26* page 546; **Dicyclomine Hydrochloride,** *USP 26* page 598; **Dimenhydrinate,** *USP 26* page 628; **Dimercaprol,** *USP 26* page 631; **Dolasetron Mesylate,** *USP 26* page 658; **Edetate Calcium Disodium,** *USP 26* page 683; **Edetate Disodium,** *USP 26* page 684; **Edrophonium Chloride,** *USP 26* page 685; **Glycopyrrolate,** *USP 26* page 869; **Histamine Phosphate,** *USP 26* page 902; **Hyoscyamine Sulfate,** *USP 26* page 941; **Metoclopramide Hydrochloride,** *USP 26* page 1217; **Dibasic Potassium Phosphate,** *USP 26* page 1517; **Pralidoxime Chloride,** *USP 26* page 1521; **Prochlorperazine Edisylate,** *USP 26* page 1551; **Ranitidine Hydrochloride,** *USP 26* page 1615; **Selenious Acid,** *USP 26* page 1675; **Sodium Bicarbonate,** *USP 26* page 1687; **Dibasic Sodium Phosphate,** *USP 26* page 1702; **Monobasic Sodium Phosphate,** *USP 26* page 1702 and page 1078 of *PF* 29(4) [July–Aug. 2003]; **Sodium Sulfate,** *USP 26* page 1705; **Sodium Thiosulfate,** *USP 26* page 1706; **Tolbutamide,** *USP 26* page 1853; **Trimethobenzamide Hydrochloride,** *USP 26* page 1891 and page 672 of *PF* 29(3) [May–June 2003]. Revisions are proposed to establish consistency with the system of *Labeling* established in 1993 by the USP Drug Nomenclature Committee, as published on page 5618 of *PF* 19(4) [July–Aug. 1993]. Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms, a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that where the label states that it is sterile it must meet the requirements under *Sterility Tests* ⟨71⟩ and *Bacterial Endotoxins Test* ⟨85⟩. In addition where the label states that it must be subjected to further processing during the preparation of injectable dosage forms it must meet the requirements under *Bacterial Endotoxins Test* ⟨85⟩. In some monographs it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-1

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩*—USP Endotoxin RS.*■2S (*USP27*)

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Add the following:

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

BRIEFING

Ammonium Molybdate, *USP 26* page 135—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-2

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

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

BRIEFING

Atenolol, *USP 26* page 185—See briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-3

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Atenolol RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

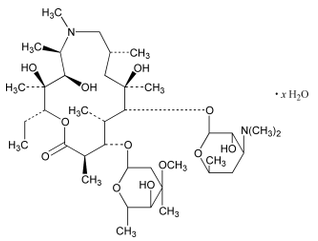
Add the following:

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

BRIEFING

Azithromycin, *USP 26* page 199 and page 50 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to provide standards of quality for Azithromycin that is in the form of the monohydrate, in addition to the current form, which is the dihydrate. It is proposed to revise the section on *Labeling* to require that the article be labeled to state whether it is the monohydrate or the dihydrate. It is proposed to provide different *Water* limits of not less than 1.8% and not more than 4.0% for the monohydrate form of Azithromycin. The theoretical *Water* content of Azithromycin (monohydrate) is 2.35%. In addition, because of the possible presence of adsorbed surface moisture, a *Loss on drying* test using the thermogravimetric technique is proposed that would reveal *Loss on drying* in two stages: the determination of surface or adsorbed water by heating it from ambient temperature to about 80°, and the loss of monohydrate between 80° and 130°. While the monohydrate may adsorb surface water, Azithromycin dihydrate does not.

(PA7a: W. Wright) RTS—39481-1; 39871-1



Change to read:

~~$C_{38}H_{72}N_2O_{12} \cdot 2H_2O$~~

■$C_{38}H_{72}N_2O_{12} \cdot xH_2O$■2S (*USP27*)
~~785.02~~

■(anhydrous) 749.00 [*83905-01-5*]■2S (*USP27*)
1-Oxa-6-azacyclopentadecan-15-one, 13-[(2,6-dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]~~-,dihydrate,~~

■■2S (*USP27*)
[2*R*(2*R**,3*S**,4*R**,5*R**,8*R**,10*R**,11*R**,12*S**,13*S**,14*R**)].
(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-13-[(2,6-Dideoxy-3-*C*-methyl-3-*O*-methyl-α-L-*ribo*-hexopyranosyl)oxy]-2-ethyl-3,4,10-trihydroxy-3,5,6,8,10,12,14-heptamethyl-11-[[3,4,6-trideoxy-3-(dimethylamino)-β-D-*xylo*-hexopyranosyl]oxy]-1-oxa-6-azacyclopentadecan-15-one.~~dihydrate.~~

■■2S (*USP27*)
9-Deoxo-9a-aza-9a-methyl-9a-homoerythromycin A.

■Monohydrate 767.02 [*121479-24-4*]■2S (*USP27*)
Dihydrate

■785.02■2S (*USP27*)
[*117772-70-0*]
~~Anhydrous 749.00 [*83905-01-5*]~~

■■2S (*USP27*)

Change to read:

» Azithromycin contains

■one or two molecules of water of hydration. It contains■2S (*USP27*)
the equivalent of not less than 945 µg and not more than 1030 µg of azithromycin ($C_{38}H_{72}N_2O_{12}$) per mg, calculated on the anhydrous basis.

Add the following:

■**Labeling—**Label it to indicate whether it is the monohydrate or the dihydrate. Where the quantity of azithromycin is indicated in the labeling of any preparation containing Azithromycin, this shall be understood to be in terms of anhydrous azithromycin ($C_{28}H_{72}N_2O_{12}$).■2S (*USP27*)

Change to read:
USP Reference standards ⟨11⟩—*USP Azithromycin RS. USP Azaerythromycin A RS.*

■*USP Desosaminylazithromycin RS. USP N-Demethylazithromycin RS.*■2S (*USP27*)

Change to read:
Water, *Method I* ⟨921⟩: between 4.0% and 5.0%

■where it is labeled as the dihydrate; between 1.8% and 4.0% where it is labeled as the monohydrate, except that it may be between 4.0% and 6.5% when the requirements of the *Loss on drying* test are met.■2S (*USP27*)

Add the following:

■**Loss on drying** (where it is labeled as Azithromycin monohydrate and has a *Water* content of between 4.0% and 6.5%) (see *Thermal Analysis* ⟨891⟩)—[NOTE—The quantity taken for the determination may be adjusted, if necessary, for instrument sensitivity.] Determine the percentage of volatile substances by thermogravimetric analysis in an appropriately calibrated instrument, using about 10 mg of Azithromycin, accurately weighed. Heat the specimen at the rate of 10° per minute between ambient temperature and 150° in an atmosphere of nitrogen at a flow rate of 100 mL per minute. From the thermogram determine the accumulated loss in weight between ambient temperature and

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about 80° on the plateau, and from 80° to 130°: it loses not more than 4.5% of its weight between ambient temperature and about 80°, and between 1.8% and 2.6% between 80° and 130°.■2S (*USP27*)

Add the following:

▲**Limit of related substances—**[NOTE—Use water that has a resistivity of not less than 18 Mohm-cm.]

Mobile phase—Proceed as directed in the *Assay.*

pH 7.5 Potassium phosphate buffer—Transfer 2.7 g of monobasic potassium phosphate to a 1000-mL volumetric flask. Dilute with water to volume, and mix. Adjust with 10 N potassium hydroxide to a pH of 7.5 ± 0.1.

Dilution solution—Prepare a mixture of *pH 7.5 Potassium phosphate buffer* and acetonitrile (750:250).

Standard stock solution—Dissolve accurately weighed quantities of USP Desosaminylazithromycin RS, USP *N*-Demethylazithromycin RS, and USP Azithromycin RS quantitatively with acetonitrile to obtain a solution having known concentrations of about 45, 105, and 160 µg per mL, respectively.

Standard solution—Transfer 4.0 mL of *Standard stock solution* to a 200-mL volumetric flask, dilute with *Dilution solution* to volume, and mix. This solution contains known concentrations of USP Desosaminylazithromycin RS, USP *N*-Demethylazithromycin RS, and USP Azithromycin RS of about 0.9, 2.1, and 3.2 µg per mL, respectively.

Test solution—Transfer about 33 mg of Azithromycin, accurately weighed, to a 100-mL volumetric flask, add 5 mL of acetonitrile, and sonicate for about 20 seconds to dissolve. Dilute with *Dilution solution* to volume, and mix. [NOTE—Use this solution within 6 hours.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with an amperometric electrochemical detector with dual glassy carbon electrodes operated in the oxidative screen mode with electrode 1 set at +0.70 ± 0.05 V and electrode 2 set at +0.85 ± 0.05 V , and the background current optimized to 95 ± 25 nanoamperes, a 4.6-mm × 5-cm guard column that contains 5-µm packing L29, and a 4.6-mm × 15-cm analytical column that contains 5-µm packing L29 or 3-µm packing L49 without the guard column. [NOTE—In general, maintain electrode 1 at 0.12 V less than electrode 2, and maintain the electrodes at a constant temperature of about 26°.] The flow rate is about 0.4 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.38 for desosaminylazithromycin, 0.54 for *N*-demethylazithromycin, and 1.0 for azithromycin; the column efficiency is not less than 1500 theoretical plates for the azithromycin peak; the tailing factor for each of these compounds is not more than 1.5; and the relative standard deviation for replicate injections is not more than 5% for each of these compounds.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, using an elution period for the *Test solution* that is 3.3 times the elution time of the azithromycin peak in the chromatogram of the *Standard solution,* and measure the areas for all of the peaks. Calculate the percentages of desosaminylazithromycin and *N*-demethylazithromycin in the Azithromycin taken by the formula:

$$0.1(CP/W)(r_i / r_S),$$

in which C is the concentration, in µg per mL, of the appropriate USP Reference Standard in the *Standard solution; P* is the designated potency, in percentage, of the relevant Reference Standard; W is the weight, in mg, of Azithromycin taken to prepare the *Test solution;* and r_i and r_S are the peak area responses for the relevant analyte in the chromatograms

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obtained from the *Test solution* and the *Standard solution,* respectively. Calculate the percentages of other related substances in the Azithromycin taken by the formula:

$$0.01(CP/W)(r_i/r_S),$$

in which C is the concentration, in µg per mL, of USP Azithromycin RS in the *Standard solution; P* is the designated purity, in µg per mg, of USP Azithromycin RS; W is the weight, in mg, of Azithromycin taken to prepare the *Test solution;* r_i is the peak area response for an individual related substance peak in the chromatogram obtained from the *Test solution;* and r_S is the peak area response for the azithromycin peak in the chromatogram obtained from the *Standard solution.* Not more than 0.3% of desosaminylazithromycin, 0.7% of *N*-demethylazithromycin, and 1.0% of any other individual related substance is found, and the sum of all related substances is not more than 3.0%.▲*USP27*

BRIEFING

BCG Live. Because there is no existing *USP* monograph for this article, a new monograph is being proposed.

(VVI: L. Bhattacharyya) RTS—40073-1; 40074-1; 40075-1; 40076-1

Add the following:

■BCG Live

» BCG Live is a freeze-dried preparation of attenuated live bacteria derived from a culture of Bacillus Calmette-Guérin (*Mycobacterium bovis,* var. BCG) and used in the treatment of carcinoma *in situ* and papilloma tumors of the urinary bladder. The bacteria are grown in a medium that does not contain substances known to cause toxic or allergic reactions in human beings or to cause the bacteria to become virulent for guinea pigs. The culture is harvested and formulated to contain one or more excipients. The freeze-dried preparation is reconstituted and diluted further aseptically with a sterile diluent for use. A reconstituted dose contains 1.0–19.2 $\times 10^8$ cfu. BCG Live does not contain a preservative.

Packaging and storage—Preserve in single-dose hermetic Type I glass containers and store at a temperature between 2° and 8° away from direct sunlight. Do not freeze.

Expiration date—The product is stable for 1 year when stored between 2° and 8°.

Labeling—Label it to indicate the dry weight of bacteria in a vial, cfu per dose, storage conditions, expiration date, and that it is not to be used after the expiration date given on the package. Label it to state that it should be protected from direct sunlight and that it should be used immediately after reconstitution/dilution. Label it to indicate that it is for intravesical use and "Rx only."

Identification—

Carbol fuchsin solution—Transfer 10 g of basic fuchsin powder and 100 mL of alcohol to a 100-mL bottle. Mix using a magnetic stir bar and a magnetic stirrer to dissolve. Transfer the solution to a 1-L Erlenmeyer flask. Add 50 mL of Liquefied Phenol and 850 mL of water. Mix, and filter. Store at room temperature. [NOTE—The solution is stable up to 3 months when stored at ambient temperature.]

Acid–alcohol solution—Transfer 970 mL of alcohol to a 1-L bottle, add 30 mL of hydrochloric acid, and mix. Store at room temperature. [NOTE—The solution is stable up to 3 months when stored at ambient temperature.]

Methylene blue solution—Transfer 4.5 g of methylene blue to a 2-L Erlenmeyer flask, and add 450 mL alcohol. Add 150 mg of potassium hydroxide and 1500 mL of water to the flask. Mix until the solutes dissolve and filter. Store at ambient temperature. [NOTE—The solution is stable up to 1 year when stored at ambient temperature.]

Standard suspension—Use approved U.S. Reference BCG Live.

Test suspension—Reconstitute the freeze-dried BCG Live according to the manufacturer's instructions for human use with the diluent recommended by the manufacturer.

Negative control—Use the diluent recommended by the manufacturer for reconstitution of BCG Live.

Procedure—Prepare a suitable bacteriological loop and flame it where it joins the handle until it is red-hot. Allow the loop to cool down to room temperature without touching anything. Transfer a loop-full of each of the *Standard suspension,* the *Test suspension,* and the *Negative control* on separate slides. Wash the loop in a stream of water, flame it, and allow it to cool down as described above in between the transfers. [NOTE—Alternatively separate loops may be used for the transfer of different solutions.] Heat-fix each slide by passing it over a flame four times. [NOTE—Too much heat may cause the slide to break.] Flood the slides with the *Carbol fuchsin solution,* and heat them over a steam bath for about 5 minutes. [NOTE—Make sure that the entire slide is covered with the *Carbol fuchsin solution* throughout the staining procedure.] Rinse the slides with water. Flood the slides with the *Acid–alcohol solution* until no more color comes out and the slides are clear of stain visible to the naked eye (about 30 seconds). Rinse the slides thoroughly with water and drain any excess water from the slides. Flood the slides with the *Methylene blue solution* for about 30 seconds to 1 minute, and rinse them with water. Examine the slides under a microscope. Bacteria in the *Standard suspension* and the *Test suspension* stain red, and the negative control is colorless. The morphological characteristics of the stains from the *Test suspension* are similar to those from the *Standard suspension*.

Safety—It meets the requirements as set forth for *Safety Tests—Biologicals* under *Biological Reactivity Tests, In Vivo* ⟨88⟩.

Sterility ⟨71⟩— It meets the requirements when tested as directed for *Direct Inoculation of the Culture Medium* under *Test for Sterility of the Product to be Examined.*

Virulent mycobacteria—

Test suspension—Reconstitute the freeze-dried BCG Live according to the manufacturer's instructions for human use with the diluent recommended by the manufacturer and dilute aseptically to about 5 mg per mL with sterile 0.9% sodium chloride solution.

Procedure—Randomly select not less than six guinea pigs (male or female), each weighing 250 to 300 g. Inject each animal with 1.0 mL of the *Test suspension* intramuscularly in the rear left internal thigh, and observe them for a period of 6 weeks. Note the number of animals that survive at the end of the observation period, and then sacrifice them. Perform autopsies of all animals post mortem to examine them for microscopic tuberculous infections, particularly at the popliteal and inguinal lymph nodes, lungs, as well as at the injection site. If the results are not conclusive, perform a histological examination following the procedure described in *Identification,* except for the following: suitable tissue sections are used instead of the *Test suspension,* no *Standard suspension* is required, and the tuberculous infections are demonstrated by red stains in a blue background. [NOTE—The blue color is due to the staining of the nonacid-fast cells by methylene blue.] At the end of the observation period, not less than two-thirds of the animals survive; no

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sign of tuberculosis is detected in animals that survive, as well as those that died; and the animals that survive gain weight.

Skin reactivity—

Test suspensions—Reconstitute the freeze-dried BCG Live according to the manufacturer's instructions for human use with the diluent recommended by the manufacturer. Dilute the solution further 1:10, 1:100, and 1:1000 aseptically using the same diluent.

Procedure—Randomly select four guinea pigs (male or female), each weighing 250 to 300 g. Inject 0.1 mL of each of the four suspensions intradermally at different sites on the back of each animal. After 4 weeks, the animals are shaved so that the injection sites and any reactions are made clearly visible. The diameters of the reactions are measured and the presence of necrosis or nodules noted. The reaction for the largest dose is between 4 and 10 mm and the smallest dose inducing no nodule. Each animal gains weight during the observation period.

Tuberculin sensitivity—

Tuberculin solution—Use tuberculin, purified protein derivative, solution containing 25 U.S. Tuberculin Units per 0.1 mL. Dilute aseptically, if necessary, with sterile 0.9% sodium chloride solution.

Procedure—Perform on the same animals on which the *Skin reactivity* test is performed. After the *Skin reactivity* test is completed, inject each animal intradermally with 0.1 mL of the *Tuberculin solution* on the back and observe after 18 to 24 hours. An erythematous reaction of not less than 10 mm in diameter is measured on each animal.

Residual moisture, *Method Ic* ⟨921⟩: Not more than 2.5%.

Viability—Determine the potencies of BCG Live using not less than 5 containers before freeze-drying and an equal number of containers after freeze-drying, following the procedure described under *Potency,* except use the vaccine before freeze-drying as is. The loss in viability due to freeze-drying is not more than 90%.

Potency—

Culture medium—Prepare the culture medium as described below: Dissolve, adjust the pH to 7.0 with a sodium hydroxide solution, and sterilize by filtration.

Components	Weight
Asparagine	5.0 g
Monobasic potassium phosphate	5.0 g
Potassium sulfate	0.5 g
Magnesium citrate	1.5 g
Monosodium glutamate	19.0 g
Glycerin	20.0 mL
Water	900.0 mL
5% aqueous solution of albumin bovine serum	100.0 mL

Agar solution—Transfer 1.5 g of agar to an Erlenmeyer flask and add 100 mL of water. Close the mouth airtight with a suitable cotton plug and autoclave at 120° for 15 to 30 minutes. With the mouth tightly closed by the cotton plug, cool the solution to 42° and maintain in a water bath at 42° until use.

Test suspensions—Reconstitute not less than 5 containers of the freeze-dried BCG Live according to the manufacturer's instructions for human use with the diluent recommended by the manufacturer.

Procedure—[NOTE—Work in a laminar-flow biological safety cabinet under aseptic conditions.] Transfer 4.5 mL of the *Culture medium* to each of a series of 16 mm × 125 mm screw-capped test tubes. Arrange the tubes in rows such that each row contains 10 tubes. Mark the tubes from 1 to 10. Add 0.5 mL of thoroughly mixed *Test suspension* from one container to the first test tube (Tube number 1)

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of a row, mix, and transfer 0.5 mL to the next test tube (Tube number 2). Mix thoroughly and transfer 0.5 mL to the next test tube (Tube number 3). Repeat the process of mixing and serially transferring to each consecutive tube and discard 0.5 mL from the last test tube. Repeat the same process to serially dilute reconstituted vaccine from the other containers such that the reconstituted vaccine from each container can be diluted serially along separate rows. From each row select the test tube that is expected to contain 10 to 50 cfu, and the test tubes that have immediately higher and immediately lower cfu, and incubate them in a water bath at 42° for about 10 minutes. Add 0.5 mL of *Agar solution* to each test tube, mix thoroughly, transfer on a sterile 0.5% agar-gel plate, and immediately spread the solution uniformly on the plate. Incubate the plates at 35° to 37° for 3 to 4 weeks. For each container, count the number of colonies on the plates that contain between 10 to 50 of them and calculate the cfu in each container.■2S (*USP27*)

BRIEFING

Benazepril Hydrochloride, page 1768 of *PF* 28(6) [Nov.–Dec. 2002]. This new monograph is presented again with changes proposed by the innovator firm. It is proposed to include *Absorbance of solution* and *Absorbtivity* sections, and a test for chlorides in the *Identification* section. It is also proposed to modify *Test 2, Related compounds* section, to include benazepril related compounds C, D, E, F, and G, and to specify their limits. The proposed method is based on the analyses performed with the µBondapak C-18 brand of L1 column; the typical retention time for benazepril hydrochloride is 6.5 minutes. The storage statement is amended according to PSD guidelines.

(PA5: A.Wilk) RTS—39650-1

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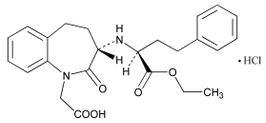
Add the following:

■Benazepril Hydrochloride



$C_{24}H_{28}N_2O_5 \cdot HCl$ ~~460.96~~ 460.95

1 *H*-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, monohydrochloride, [*S*-(*R**,*R**)]-.

(3*S*)-3-[[(1*S*)-1-Carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, 3-ethyl ester, monohydrochloride [*86541-74-4*].

» Benazepril Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{28}N_2O_5 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store at a temperature below 30°, preferably between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Benazepril Hydrochloride RS. USP Benazepril Related Compound A RS. USP Benazepril Related Compound B RS. USP Benazepril Related Compound C RS. USP Benazepril Related Compound D RS. USP Benazepril Related Compound E RS. USP Benazepril Related Compound F RS. USP Benazepril Related Compound G RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩.

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

C: It responds to the test for *Chloride* ⟨191⟩.

Absorbance of solution—The absorbance of a 1 in 100 solution of it in methanol, determined in a 2-cm cell at 420 nm, is not more than 0.03, methanol being used as the blank.

Absorbtivity—

Test Preparation: 25 mg in 1000 mL of methanol.

Procedure—Proceed as directed under *Spectrophotometry and Light-Scattering* ⟨851⟩, and measure the absorbance at 238 nm: the absorptivity is between 21.0 and 23.2.

~~**Specific rotation** ⟨781S⟩: between −136° and −141°, determined at 20°.~~

~~*Test solution:* 10 mg per mL, in dehydrated alcohol.~~

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than ~~1.5%~~ 0.5% of its weight.

Residue on ignition ⟨281⟩—Ignite at 600°. Not more than 0.1% residue is found.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

~~**Limit of ethyl acetate**~~

~~*Standard solution*~~ ~~Pipet 0.5 mL of ethyl acetate into a 100-mL volumetric flask, and determine the weight added by difference. Dissolve in and dilute with dimethylformamide to volume, and mix. Pipet 3.0 mL of this solution into a 25-mL volumetric flask, dilute with dimethylformamide to volume, and mix. Pipet 1.0 mL of this solution into a 10-mL volumetric flask, dilute with dimethylformamide to volume, and mix.~~

~~*Test solution*~~ ~~Transfer 100 mg of Benazepril Hydrochloride, accurately weighed, to a 1-mL volumetric flask. Dissolve in and dilute with dimethylformamide to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)~~ ~~The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 1.8-m glass column packed with support S1 S2. The carrier gas is helium, flowing at a rate of 30 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is equilibrated at 160° for 8 minutes, then the temperature is increased at a rate of 20° per minute to 200°, and maintained at 200° for 20 minutes. The injection port temperature is maintained at 120°, and the detector is maintained at 270°.~~

~~*Procedure*~~ ~~Separately inject equal volumes (about 2 µL) of the *Standard solution,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage, by weight, of ethyl acetate in the portion of Benazepril Hydrochloride taken by the formula:~~

$$~~0.012(W_S/W_U)(r_U/r_S),~~$$

~~in which W_S is the weight, in mg, of ethyl acetate taken to prepare the *Standard solution;* W_U is the weight, in mg, of Benazepril Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak responses of ethyl acetate obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of ethyl acetate is found.~~

~~**Limit of chloroform and alcohol**~~

~~*Standard solution*~~ ~~Pipet 0.5 mL each of chloroform and alcohol into separate 100-mL volumetric flasks, and determine the weight of each by difference. Dissolve in and dilute the contents of each flask with dimethylformamide to volume, and mix. Pipet 2.0 mL of each of these solutions into a 100-mL volumetric flask, dilute with dimethylformamide to volume, and mix.~~

~~*Test solution*~~ ~~Prepare as directed for *Test solution* under *Limit of ethyl acetate.*~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)~~ ~~Proceed as directed for *Limit of ethyl acetate*, except to increase the column temperature from 160° to 300° 200°, and maintain at 300° 200° for 30 minutes.~~

~~*Procedure*~~ ~~Separately inject equal volumes (about 2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the~~

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~~areas for the major peaks. Separately calculate the percentages, by weight, of chloroform and alcohol in the portion of Benazepril Hydrochloride taken by the formula:~~

~~$0.02(W_S / W_U)(r_U / r_S)$,~~

~~in which W_S is the weight, in mg, of either chloroform or alcohol taken to prepare the *Standard solution*; W_U is the weight, in mg, of Benazepril Hydrochloride taken to prepare the *Test solution*; and r_U and r_S are the peak responses of either chloroform or alcohol obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% 0.1% of chloroform is found; and not more than 0.1% 0.5% of alcohol is found.~~

Related compounds—

TEST 1 *(for benazepril related compound A)—*

~~*Zinc sulfate solution*—Dissolve 0.719 g of zinc sulfate heptahydrate in sufficient water to make 1000 mL. Dilute 100 mL of this solution with water to 1000 mL, and mix.~~

pH 6.0 Phosphate buffer—Dissolve 9.66 g of monobasic potassium phosphate and 2.68 g of dibasic sodium phosphate, heptahydrate in about 900 mL of water, and dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of ~~*Zinc sulfate solution* and dehydrated alcohol (975:25).~~ *pH 6.0 Phosphate buffer* and methanol (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Benazepril stock solution*—Dissolve an accurately weighed quantity of USP Benazepril RS in *Zinc sulfate solution* to obtain a solution having a known concentration of about 0.5 mg per mL.~~

Resolution solution—~~Pipet 25.0 mL of *Benazepril stock solution* and 25.0 mL of *Standard solution* into a suitable flask, and mix. Prepare a mixture of *Benazepril stock solution* and *Standard solution* (1:1).~~ Dissolve an accurately weighed quantity of USP Benazepril Hydrochloride RS and USP Benazepril Related Compound A RS in *Mobile phase,* and dilute quantitatively and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL and 0.005 mg per mL, respectively.

Standard stock solution—Dissolve an accurately weighed quantity of USP Benazepril Related Compound A RS in ~~*Zinc sulfate solution*~~ *Mobile phase* to obtain a solution having a known concentration of about ~~0.5 mg~~ 0.05 mg per mL.

Standard solution—Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 5 µg per mL.

Dilute standard solution—~~Pipet 1.0 mL of the *Standard solution* into a 100-mL volumetric flask, and dilute with *Benazepril stock solution* to volume.~~ Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 1 µg per mL.

Test solution—Transfer about 50 mg of Benazepril Hydrochloride, accurately weighed, to a ~~100-mL~~ 50-mL volumetric flask, dissolve in and dilute with ~~*Zinc sulfate solution*~~ *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a ~~4.6-mm × 25-cm~~ 4.0-mm × 10-cm column that contains packing ~~L32.~~ L41. The flow rate is about ~~1 mL~~ 0.9 mL per minute. The column temperature is maintained at ~~50°.~~ 30°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about ~~1.8~~ 2.3 for benazepril related compound A and 1.0 for benazepril hydrochloride; and the resolution, *R,* between benazepril hydrochloride and benazepril related compound A is not less than ~~5.0.~~ 2.0. Chro-

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matograph the *Dilute standard solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is ~~greater~~ not less than 10:1. Chromatograph the *Standard solution:* the relative standard deviation for replicate injections determined from the benazepril ~~hydrochloride~~ related compound A peak is not more than ~~3.5%.~~ 10%.

Procedure—Separately inject equal volumes (about 50 µL) of the ~~*Dilute standard*~~ *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the ~~areas for all the peaks.~~ area for the benazepril related compound A peak. Calculate the percentage of benazepril related compound A in the portion of Benazepril Hydrochloride taken by the formula:

$$100(C_S / C_T)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Benazepril Related Compound A RS in the ~~*Dilute standard*~~ *Standard solution;* C_T is the concentration, in mg per mL, of Benazepril Hydrochloride in the *Test solution;* r_U is the peak response for benazepril related compound A obtained from the *Test solution;* and r_S is the peak response for benazepril related compound A obtained from the ~~*Dilute standard*~~ *Standard solution:* not more than ~~0.5%~~ 0.1% of benazepril related compound A is found.

TEST 2 *(for benazepril related compound B, ~~and other impurities)~~ C, D, E, F, and G)—*

Tetrabutylammonium bromide solution, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—~~Pipet 5.0 mL of *System suitability solution* into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~ Dissolve accurately weighed quantities of USP Benazepril Related Compound B RS, USP Benazepril Related Compound C RS, USP Benazepril Related Compound D RS, USP Benazepril Related Compound E RS, USP Benazepril Related Compound F RS, and USP Benazepril Related Compound G RS in *Mobile phase* to obtain a solution having known concentrations of about 10 µg per mL of each related compound.

Test solution—Transfer about ~~100~~ 50 mg of Benazepril Hydrochloride, accurately weighed, to a ~~100-mL~~ 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas for ~~benazepril related compound B.~~ all the peaks. Calculate the percentage of benazepril related compounds ~~B~~ in the portion of Benazepril Hydrochloride taken by the formula:

$$100(C_S / C_T)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of ~~USP Benazepril Related Compound B RS~~ the relevant Reference Standard in the *Standard solution;* C_T is the concentration, in mg per mL, of benazepril hydrochloride in the *Test solution;* r_U is the peak response for the relevant benazepril related compound ~~B~~ obtained from the *Test solution;* and r_S is the peak response for the relevant benazepril related compound ~~B~~ obtained from the *Standard solution* (See *Table 1* for values). ~~not more than 1.0% of benazepril related compound B is found. Calculate the percentage of each impurity (other than benazepril related compound B) in the portion of Benazepril Hydrochloride taken by the formula:~~

~~$100(F r_i / r_S),$~~

~~in which *F,* the relative response factor, is equal to 0.53, 0.66, and 0.86 for peaks with relative retention times of 0.43, 0.51, and 0.60, respectively, and 1.0 for all other peaks; 0.4 [(3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benazepine)-1-acetic acid], 0.5 [*t*-butyl-(3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benazepine)-1-acetate], and~~

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~~0.6 [(3-(1-carboxy-3-phenyl-1*S*-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benazepine)-1-acetic acid], respectively, and 1.0 for all other peaks including peaks at relative retention times of 1.8 [(3-(1-ethoxyearbonyl-3-cyclohexyl-1*S*-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benazepine)-1-acetic acid] and 2.1 [ethyl (3-(1-ethoxycarbonyl-3-phenyl-1*S*-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benazepine)-1-acetic acid]; *r*$_i$ is the peak response for each impurity obtained from the *Test solution;* and *r*$_s$ is the sum of the responses of all the peaks: not more than 0.5% of any impurity is found; and not more than 2.0% of total impurities is found, the results of *Test 1* and *Test 2* being added.~~

Table 1

Relative Retention Time	Benazepril Related Compound	Limit (%)
0.4	E[1]	0.2
0.5	F[2]	0.2
0.6	C[3]	0.3
1.5	B[4]	0.5
1.7	D[5]	0.2
2.0	G[6]	0.2

[1] 3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid

[2] t-butyl-3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid

[3] (3-(1-carboxy-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid

[4] Mixture of diastereoisomers (3-(1-ethoxycarbonyl-3-phenyl-(1*R*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid and and (3-(1-ethoxycarbonyl-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*R*)-benzazepine)-1-acetic acid

[5] (3-(1-ethoxycarbonyl-3-cyclohexyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid

[6] (3-(1-ethoxycarbonyl-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid ethyl ester

In addition to not exceeding the limits for benazepril related compounds in *Table 1*, not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities (excluding benazepril related compound A from *Test 1*) is found.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Solvent: dimethylformamide.

Assay—

Tetrabutylammonium bromide solution—Dissolve 0.81 g of tetrabutylammonium bromide in 360 mL of water containing 0.2 mL of glacial acetic acid.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Tetrabutylammonium bromide solution* ~~(2:1).~~ (64:36). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Benazepril Hydrochloride RS and USP Benazepril Related Compound B RS in *Mobile phase* to obtain a solution having known concentrations of about ~~0.2 mg~~ 0.4 mg of each per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Benazepril Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.2 mg per mL.

Assay preparation—Transfer about ~~50 mg~~ 10 mg of Benazepril Hydrochloride, accurately weighed, to a ~~250-mL~~ 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 0.3-cm guard column that contains ~~7-µm~~ packing L1 connected to a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and

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record the peak responses as directed for *Procedure:* ~~the relative retention times are about 1.5 for benazepril related compound B and 1.0 for benazepril hydrochloride;~~ the resolution, *R,* between benazepril hydrochloride and benazepril related compound B is not less than ~~4.0;~~ 1.7 and the relative standard deviation for replicate injections determined from benazepril hydrochloride and benazepril related compound B is not more than ~~1.0%~~ 2.0% for each.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg, of $C_{24}H_{28}N_2O_5 \cdot HCl$ in the portion of Benazepril Hydrochloride taken by the formula:

$$250C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Benazepril Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Betamethasone, *USP 26* page 232 and page 3083 of the *Second Supplement;* **Betamethasone Acetate,** *USP 26* page 235 and page 3083 of the *Second Supplement;* **Betamethasone Benzoate,** *USP 26* page 235; **Betamethasone Benzoate Gel,** *USP 26* page 236. It is proposed to add appropriate storage temperatures to the *Packaging and storage* section to conform to the policy established by the USP Packaging, Storage, and Distribution Expert Committee.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40165-1

Change to read:

Packaging and storage—~~Preserve in well-closed containers.~~

■Store between 2° and 30° in a tight container.■2S (*USP27*)

BRIEFING

Betamethasone Acetate, *USP 26* page 235 and page 3083 of the *Second Supplement*—See briefing under *Betamethasone*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40166-1

Change to read:

Packaging and storage—~~Preserve in tight containers.~~

■Store between 2° and 30° in a tight container.■2S (*USP27*)

BRIEFING

Betamethasone Benzoate, *USP 26* page 235—See briefing under *Betamethasone*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40169-1

Change to read:

Packaging and storage—~~Preserve in tight containers.~~

■Store between 2° and 30° in a tight container.■2S (*USP27*)

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BRIEFING

Betamethasone Benzoate Gel, *USP 26* page 236—See briefing under *Betamethasone*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40170-1

Change to read:

Packaging and storage—~~Preserve in collapsible tubes or in tight containers.~~

■Store at 25°, excursions permitted between 15° and 30°. Store in a tight container. Protect from freezing.■2S (*USP27*)

BRIEFING

Betamethasone Dipropionate, *USP 26* page 236; **Betamethasone Dipropionate Topical Aerosol,** *USP 26* page 237; **Betamethasone Dipropionate Cream,** *USP 26* page 237; **Betamethasone Dipropionate Lotion,** *USP 26* page 238; **Betamethasone Dipropionate Ointment,** *USP 26* page 238. The proposed revision to the *Packaging and storage* statement conforms to the policy established by the USP Packaging, Storage, and Distribution Expert Committee.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40210-1

Change to read:

Packaging and storage—~~Preserve in well-closed containers.~~

■Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Betamethasone Dipropionate Topical Aerosol, *USP 26* page 237. It is proposed to update the style of the *Identification* test according to the general test chapter *Thin-Layer Chromatographic Identification Test* ⟨201⟩. See also the briefing under *Betamethasone Dipropionate*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40216-1

Change to read:

Packaging and storage—Preserve in tight, pressurized containers, and avoid exposure to excessive heat.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

~~**Identification**—~~

■**Thin-layer chromatographic identification test** ⟨201⟩—■2S (*USP27*)

~~Place the container in a dry ice–methanol bath for about 5 minutes. Open the can by means of a tube-cutter, and allow the propellant to evaporate under a gentle stream of nitrogen for about 1 hour. Transfer about 3 mL of the residue to a 50-mL centrifuge tube. Add 10 mL of a mixture of methanol and water (4:1), and shake vigorously. Centrifuge to clarify. Proceed as directed in *Identification* test *B* under *Betamethasone Valerate*, but apply 25 µL of this solution and 25 µL of a solution of USP Betamethasone Dipropionate RS in methanol containing about 3.2 mg per mL.~~

■*Test solution*—Place the container in a dry ice–methanol bath for about 5 minutes. Open the can by means of a tube-cutter, and allow the propellant to evaporate under a gentle stream of nitrogen for about 1 hour. Transfer about 3 mL of the residue to a 50-mL centrifuge tube. Add 10 mL of a mixture of methanol and water (4:1), and shake vigorously. Centrifuge to clarify.

Standard solution: USP Betamethasone Dipropionate RS in methanol containing 3.2 mg per mL.

Application volume: 25 µL.

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Developing solvent system: a mixture of toluene and ethyl acetate (1:1).

Procedure—Proceed as directed in the chapter. Spray the plate with a mixture of sulfuric acid, methanol, and nitric acid (10:10:1), and heat at 105° for 15 minutes.■2S (*USP27*)

BRIEFING

Betamethasone Dipropionate Cream, *USP 26* page 237. It is proposed to update the style of the *Identification* test according to the general test chapter *Thin-Layer Chromatographic Identification Test* ⟨201⟩. See also the briefing under *Betamethasone Dipropionate*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40219-1

Change to read:

Packaging and storage—Preserve in collapsible tubes or in tight containers.

■Store at 25°, excursions permitted between 15° and 30°. Protect from freezing.■2S (*USP27*)

Change to read:

~~**Identification—**~~

■Thin-layer chromatographic identification test ⟨201⟩—■2S (*USP27*)

~~Transfer about 1.5 g of Cream to a glass-stoppered, 50-mL centrifuge tube. Add 15 mL of methanol-hydrochloric acid solution prepared by mixing 1 volume of dilute hydrochloric acid (1 in 120) with 4 volumes of methanol. Shake to obtain a homogeneous mixture. Add 30 mL of solvent hexane, mix for 10 minutes, and centrifuge. Using a suitable syringe, transfer the lower aqueous phase to a second centrifuge tube, add about 20 mL of water, and mix. Extract this aqueous mixture with chloroform by shaking, centrifuging, and removing the lower, chloroform phase with a syringe. Evaporate the chloroform on a steam bath with the aid of a stream of nitrogen to dryness, cool, and dissolve the residue in chloroform to obtain a solution containing about 150 µg of betamethasone dipropionate per mL. Apply 40 µL of this solution and 40 µL of a Standard solution of USP Betamethasone Dipropionate RS in chloroform containing 150 µg per mL to a suitable thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel mixture. Allow the spots to dry, and develop the chromatograph in a solvent system consisting of a mixture of chloroform and acetone (7:1) until the solvent has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Observe the dried spots under a short-wavelength (254-nm) UV light source: the R_F value of the principal spot obtained from the test solution corresponds to that obtained from the Standard solution.~~

■*Test solution*—Transfer about 1.5 g of Cream to a glass-stoppered, 50-mL centrifuge tube. Add 15 mL of a methanol–hydrochloric acid solution prepared by mixing 1 volume of dilute hydrochloric acid (1 in 120) with 4 volumes of methanol. Shake to obtain a homogeneous mixture. Add 30 mL of solvent hexane, mix for 10 minutes, and centrifuge. Using a suitable syringe, transfer the lower aqueous phase to a second centrifuge tube, add about 20 mL of water, and mix. Extract this aqueous mixture with chloroform by shaking, centrifuging, and removing the lower, chloroform phase with a syringe. Evaporate the chloroform on a steam bath with the aid of a stream of nitrogen to dryness, cool, and dissolve the residue in chloroform to obtain a solution containing about 150 µg of betamethasone dipropionate per mL.

Standard solution: USP Betamethasone Dipropionate RS in chloroform containing 150 µg per mL.

Application volume: 40 µL.

Developing solvent system: a mixture of chloroform and acetone (7:1).

Procedure—Proceed as directed in the chapter.■2S (*USP27*)

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BRIEFING

Betamethasone Dipropionate Lotion, *USP 26* page 238. It is proposed to update the style of the *Identification* test according to the general test chapter *Thin-Layer Chromatographic Identification Test* ⟨201⟩. See also the briefing under *Betamethasone Dipropionate*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40220-1

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°. Protect from light and freezing.■2S (*USP27*)

Change to read:

~~**Identification—**~~

■Thin-layer chromatographic identification test ⟨201⟩—■2S (*USP27*)

~~Transfer a quantity of Lotion, equivalent to about 0.6 mg of betamethasone dipropionate, to a 50-mL vial. Add 10 mL of 0.1 N hydrochloric acid, then add 4 mL of chloroform. Disperse on a vortex mixer for about 1 minute, then shake vigorously for 10 minutes, and centrifuge at 2000 rpm for about 5 minutes. Transfer the chloroform layer to a suitable vial. Proceed as directed in the *Identification* test under *Betamethasone Dipropionate Cream,* beginning with "Apply 40 µL of this solution."~~

■*Test solution*—Transfer a quantity of Lotion, equivalent to about 0.6 mg of betamethasone dipropionate, to a 50-mL vial. Add 10 mL of 0.1 N hydrochloric acid, then add 4 mL of chloroform. Disperse on a vortex mixer for about 1 minute, then shake vigorously for 10 minutes, and centrifuge at 2000 rpm for about 5 minutes. Transfer the chloroform layer to a suitable vial.

Standard solution: USP Betamethasone Dipropionate RS in chloroform containing 150 µg per mL.

Application volume: 40 µL.

Developing solvent system: a mixture of chloroform and acetone (7:1).

Procedure—Proceed as directed in the chapter.■2S (*USP27*)

BRIEFING

Betamethasone Dipropionate Ointment, *USP 26* page 238. It is proposed to update the style of the *Identification* test according to the general test chapter *Thin-Layer Chromatographic Identification Test* ⟨201⟩. See also the briefing under *Betamethasone Dipropionate*.

(PA1: C. Anthony; PSD: C. Okeke) RTS—40221-1

Change to read:

Packaging and storage—Preserve in collapsible tubes or in ~~well-closed containers.~~

■tight containers. Store at 25°, excursions permitted between 15° and 30°. Protect from freezing.■2S (*USP27*)

Change to read:

~~**Identification—**~~

■Thin-layer chromatographic identification test ⟨201⟩—■2S (*USP27*)

~~It responds to the *Identification* test under *Betamethasone Dipropionate Cream.*~~

■*Test solution*—Transfer about 1.5 g of Ointment to a glass-stoppered, 50-mL centrifuge tube. Add 15 mL of methanol–hydrochloric acid solution prepared by mixing 1 volume of dilute hydrochloric acid (1 in 120) with 4 volumes of methanol. Shake to obtain a homogeneous mixture. Add 30 mL of solvent hexane, mix for 10 minutes, and centrifuge. Using a suitable syringe, transfer the lower aqueous phase to a second centrifuge tube, add about 20 mL of water, and mix. Extract this aqueous mixture with chloroform by shaking, centrifuging, and removing the lower, chloroform phase with a syringe. Evaporate the chloroform on a steam bath with the aid of a stream of nitrogen to dryness, cool, and dissolve the residue in chloroform to obtain a solution containing about 150 µg of betamethasone dipropionate per mL.

Standard solution: USP Betamethasone Dipropionate RS in chloroform containing 150 µg per mL.

Application volume: 40 µL.

Developing solvent system: a mixture of chloroform and acetone (7:1).

Procedure—Proceed as directed in the chapter.■2S (*USP27*)

Add the following:

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

BRIEFING

Bretylium Tosylate, *USP 26* page 263—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-4

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Bretylium Tosylate RS*.

■*USP Endotoxin RS*.■2S (*USP27*)

BRIEFING

Brompheniramine Maleate, *USP 26* page 270—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-2

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Brompheniramine Maleate RS*.

■*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Bumetanide, *USP 26* page 274—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-5

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Bumetanide RS. USP Bumetanide Related Compound A RS. USP Butyl 3-(butylamino)-4-phenoxy-5-sulfamoylbenzoate RS. USP Bumetanide Related Compound B RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Bupivacaine Hydrochloride, *USP 26* page 276—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-3

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Bupivacaine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Bupivacaine Hydrochloride is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Bupivacaine Hydrochloride Injection*. Where the label states that Bupivacaine Hydrochloride must be subjected to further processing

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during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Bupivacaine Hydrochloride Injection*.■2S (*USP27*)

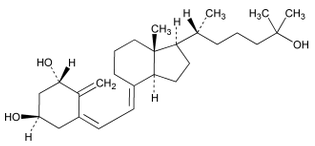
BRIEFING

Calcitriol. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the test for *Chromatographic purity* and in the *Assay* is based on analyses performed with the Symmetry or Zorbax brands of L7 column. The typical retention time for calcitriol is about 17 to 20 minutes. See also the briefing under *Calcitriol Injection*.

(PA4: E. Gonikberg) RTS—37377-1

Add the following:

■Calcitriol



$C_{27}H_{44}O_3$ 416.64

9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol, (1α,3β,5*Z*,7*E*)-.

(5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1α,3β,25-triol [*32222-06-3*].

» Calcitriol contains not less than 97.0 percent and not more than 103.0 percent of $C_{27}H_{44}O_3$, calculated on the anhydrous basis.

Caution—Care should be taken to prevent inhaling particles of Calcitriol and exposing the skin to it.

Packaging and storage—Preserve in tight, light-resistant containers, and store under nitrogen in a refrigerator between 2° and 8°.

USP Reference standards ⟨11⟩—*USP Calcitriol RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

Chromatographic purity—[NOTE—Avoid unnecessary exposure of solutions to light or air.]

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

Standard stock solution—Prepare as directed for *Standard preparation* in the *Assay.*

Standard solution—Transfer 1.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Prepare as directed for *Assay preparation* in the *Assay.*

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph; record the chromatograms for at least two times the retention time of the calcitriol peak; and measure the peak responses, disregarding any peak having an area less than 0.1 times that of the main peak in the chromatogram of the *Standard solution*. Calculate the percentage of any individual impurity in the portion of Calcitriol taken by the formula:

$$100(r_i / r_s),$$

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in which r_i is the peak response of any individual peak other than the main calcitriol peak and the precalcitriol peak; and r_s is the sum of the responses of all the peaks: not more than 0.5% of any individual impurity is found; and not more than 1.0% of total impurities is found.

Assay—[NOTE—Avoid unnecessary exposure of solutions to light or air.]

Tris buffer solution—Dissolve 1.0 g of tris(hydroxymethyl)aminomethane in 900 mL of water, adjust with phosphoric acid to a pH of 7.0 to 7.5, dilute with water to make 1000 mL, and mix.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Tris buffer solution* (55:45). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Prepare a solution of USP Calcitriol RS in *Mobile phase* (without heating) having a known concentration of about 100 µg of calcitriol per mL.

System suitability solution—Heat 2.0 mL of the *Standard preparation* at 80° for 30 minutes.

Assay preparation—Transfer about 1.0 mg of Calcitriol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume without heating, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for precalcitriol and 1.0 for calcitriol; the resolution, *R*, between precalcitriol and calcitriol is not less than 3.5; and the relative standard deviation for replicate injections, determined from the calcitriol peak, is not more than 1.0%. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 10,000 theoretical plates; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of $C_{27}H_{44}O_3$ in the portion of Calcitriol taken by the formula:

$$10C(r_U / r_S),$$

in which *C* is the concentration, in µg per mL, of calcitriol in the *Standard preparation;* and r_U and r_S are the peak responses of the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Calcitriol Injection. Because there is no existing *USP* monograph for this dosage form, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the Ultrasphere ODS brand of 5-µm L1 guard column and the Ultrasphere ODS brand of 3-µm L1 analytical column. The typical retention time for calcitriol is about 20 to 25 minutes. See also the briefing under *Calcitriol*.

(PA4: E. Gonikberg) RTS—37377-2

In-Process Revision

Add the following:

■Calcitriol Injection

» Calcitriol Injection is a terminally sterilized solution of Calcitriol. It contains an amount of Calcitriol equivalent to not less than 90.0 percent and not more than 115.0 percent of the labeled amount of calcitriol ($C_{27}H_{44}O_3$). It contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass, protected from light. Store at controlled room temperature (15° to 30°).

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Calcitriol Solution RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩—It contains not more than 100 USP Endotoxin Units per µg of calcitriol.

pH ⟨791⟩: between 5.9 and 7.0, determined on a portion to which 0.30 mL of saturated potassium chloride solution has been added for each 100 mL of Injection.

Particulate matter ⟨788⟩: meets the requirements for small-volume injections.

Aluminum ⟨206⟩: not more than 1 µg per mL.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—[NOTE—Avoid unnecessary exposure of solutions to light or air.]

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (74:26). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩) so that the retention time for calcitriol is not less than 20 minutes.

Standard preparation—Transfer 3.0 mL of USP Calcitriol Solution RS, equilibrated to room temperature, to a container, add 3.0 mL of water, and mix.

Assay preparation—Transfer an accurately measured volume of Injection, equivalent to about 3 µg of calcitriol, to a container, add a sufficient amount of water to dilute to a total volume of 3.0 mL, add 3.0 mL of methanol, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 264-nm detector, a 4.6-mm × 4.5-cm guard column that contains 5-µm packing L1; and a 4.6-mm × 7.5-cm analytical column that contains 3-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of calcitriol ($C_{37}H_{44}O_3$) in the portion of the Injection taken by the formula:

$$6C(r_U / r_S),$$

in which C is the concentration, in µg per mL, of calcitriol in the *Standard preparation,* calculated based on the content of calcitriol in the USP Calcitriol Solution RS; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

In-Process Revision

BRIEFING

Calcium Chloride, *USP 26* page 305—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-4

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Where Calcium Chloride is intended for use in hemodialysis, it is so labeled.

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Carboprost Tromethamine, *USP 26* page 339—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-2

Add the following:

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

Add the following:

■**Other requirements**—Where the label states that Carboprost Tromethamine is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Cefadroxil, *USP 26* page 353. It is proposed to simplify and improve the thin-layer chromatographic procedure in the test for *Chromatographic purity.* It has been reported that no spots were detected after developing and spraying the plate and allowing it to air dry. In addition, when the sprayed plate was heated for 20 minutes at 110°, the spots were faint and barely detected. On the other hand, it was also found that observing the unsprayed plate under short-wavelength UV light provided good visualization. It is therefore proposed to omit the spraying with ninhydrin solution and to use short-wavelength UV light for visualization. On the basis of a suggestion received, it is also proposed to include a reference solution of D-α-4-hydroxyphenylglycine to confirm the elution position of that entity. In addition, editorial style changes have been made.

(PA7: W. Wright) RTS—39819-1

Change to read:

Chromatographic purity—

Adsorbent: a 0.25-mm layer fo chromatographic silica gel mixture.

Solvent—Prepare a mixture of alcohol, water, and 2.4 N hydrochloric acid (75:22:3).

Test solution—Prepare a solution of Cefadroxil in *Solvent* containing 25 mg per mL.

Standard solution 1—Dilute 1.0 mL of the *Test solution* with *Solvent,* to 100 mL and mix.

Standard solution 2—Prepare a solution in *Solvent* containing 0.25 mg each of 7-aminodesacetoxycephalosporanic acid and D-α-4-hydroxyphenylglycine per mL.

■*Standard solution 3*—Prepare a solution in *Solvent* containing 0.25 mg of D-α-4-hydroxyphenylglycine per mL.■2S (*USP27*)

Resolution solution—Mix 1.0 mL of the *Test solution* and 1.0 mL of *Standard solution 2.*

Developing solvent system: a mixture of ethyl acetate, alcohol, water, and formic acid (14:5:5:1).

Procedure—Apply separate 2-µL portions of the *Test solution, Standard solution 1, Standard solution 2,* and

■*Standard solution 3,* and■2S (*USP27*)
a 4-µL portion of the *Resolution solution* to a suitable thin-layer chromatographic plate (see *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩), and develop the chromatograms until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, allow the plate to dry, ~~Spray the plate with a solution prepared by dissolving 3 g of ninhydrin in 100 mL of a 4.55% solution of sodium metabisulfite. Allow the plate to dry,~~

■■2S (*USP27*)
and examine the chromatograms

■under short-wavelength UV light:■2S (*USP27*)
any secondary spot in the chromatogram obtained from the *Test solution* corresponding to 7-aminodesacetoxycephalosporanic acid or D-α-4-hydroxyphenylglycine is not more intense than the corresponding spot in the chromatogram obtained from *Standard solution 2* (1.0%), and any spot, other than the principal spot and any spot corresponding to 7-aminodesacetoxycephalosporanic acid or D-α-4-hydroxyphenylglycine, is not more intense than the principal spot in the chromatogram obtained from *Standard solution 1* (1.0%). In a valid test, the chromatogram obtained from the *Resolution solution* shows three clearly separated spots.

BRIEFING

Cefepime Hydrochloride, *USP 26* page 358. It is proposed to improve the system suitability requirements in the liquid chromatographic test for *Related compounds.* Currently, the requirement for the resolution, *R,* between cefepime related compound A and cefepime related compound B is not less than 10. It is proposed to add a second resolution requirement of not less than 5 between cefepime and cefepime related compound A.

(PA7: W. Wright) RTS—39828-1

Change to read:

Related compounds~~—~~

Potassium phosphate solution—Dissolve 0.68 g of monobasic potassium phosphate in 1000 mL of water.

Solution A—Prepare a mixture of *Potassium phosphate solution* and acetonitrile (9:1). Adjust with a potassium hydroxide solution (2 in 100) to a pH of 5.0, filter, and degas.

Solution B—Prepare a mixture of *Potassium phosphate solution* and acetonitrile (1:1). Adjust with a potassium hydroxide solution (2 in 100) to a pH of 5.0, filter, and degas.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Prepare a solution of USP Cefepime Hydrochloride System Suitability RS in *Solution A* containing about 1.4 mg per mL.

Test solution—Transfer about 70 mg of Cefepime Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Solution A* to volume, sonicate, and mix. [NOTE—Inject this solution immediately, or store in a refrigerator and inject within 12 hours.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	100	0	isocratic
10–30	100→50	0→50	linear gradient
30–35	50	50	isocratic
35–36	50→100	50→0	linear gradient

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 2.7 for cefepime related compound A, 4.3 for cefepime related compound B, and 1.0 for cefepime; and the resolution, *R,*

■between cefepime and cefepime related compound A is not less than 5 and■2S (*USP27*)
between cefepime related compound A and cefepime related compound B is not less than 10. Chromatograph the *Test solution,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′,* is more than 0.6; the column efficiency is not less than 4000 theoretical plates; and the tailing factor is not more than 1.1.

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Cefepime Hydrochloride taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 0.3% of cefepime related compound A is found; not more than 0.2% of cefepime related compound B is found; and not more than 0.1% of any other impurity is found.

In-Process Revision

BRIEFING

Cefuroxime Axetil for Oral Suspension, page 3086 of the *Second Supplement to USP 26*. It is proposed to revise the liquid chromatographic *Assay* for *Cefuroxime Axetil for Oral Suspension*. It is proposed to delete the *Internal standard solution* from the method. It has been found that the main peak for acetanilide obtained with the *Internal standard solution* occurs at about the same retention time as an impurity peak in the chromatogram of the *Assay preparation* without the *Internal standard solution*. It is also proposed to add a system suitability test for resolution between cefuroxime axetil and cefuroxime axetil delta-3 isomers.

(PA7: W. Wright) RTS—39989-1

Change to read:

Assay—

0.2 M Monobasic ammonium phosphate, Mobile phase, ~~*Internal standard solution, Resolution solution, Standard preparation,*~~

■■2S (*USP27*)
and *Chromatographic system*—Proceed as directed in the *Assay* under *Cefuroxime Axetil*.

■*Resolution solution*—In a 50-mL volumetric flask, mix 10.0 mL of a solution of USP Cefuroxime Axetil RS in methanol containing 1.2 mg per mL, 5.0 mL of methanol, and 3.8 mL of a solution of USP Cefuroxime Axetil Delta-3 Isomers RS in methanol containing 0.16 mg per mL. Dilute with *0.2 M Monobasic ammonium phosphate* to volume, and mix.

Standard preparation—Transfer about 30 mg of USP Cefuroxime Axetil RS, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Promptly transfer 10.0 mL of this solution to a 50-mL volumetric flask, add 8.8 mL of methanol, dilute with *0.2 M Monobasic ammonium phosphate* to volume, and mix.■2S (*USP27*)

Assay preparation—Transfer to a 100-mL volumetric flask an accurately measured portion of Cefuroxime Axetil for Oral Suspension, freshly mixed and free from air bubbles, constituted as directed in the labeling, and equivalent to about 250 mg of cefuroxime. Add about 50 mL of methanol, and shake by mechanical means for about 10 minutes. Dilute with methanol to volume, and mix. Filter a portion of this stock solution, and transfer 5.0 mL of the filtrate to a 50-mL volumetric flask. Add ~~5.0 mL of *Internal standard solution* and 8.8 mL~~

■13.8 mL■2S (*USP27*)
of methanol, dilute with *0.2 M Monobasic ammonium phosphate* to volume, and mix. [NOTE—Protect this *Assay preparation* from light and use promptly, or refrigerate and use on the day prepared.]

Procedure—Proceed as directed in the *Assay* under *Cefuroxime Axetil*. Calculate the quantity, in mg, of cefuroxime ($C_{16}H_{16}N_4O_8S$) in each mL of Cefuroxime Axetil for Oral Suspension taken by the formula:

~~$(W_S P_S/12500V)(100-K)(R_U/R_S)$,~~

■$(W_S P_S /12{,}500V)(100 - K)(r_U / r_S)$,■2S (*USP27*)

in which V is the volume, in mL, of Cefuroxime Axetil for Oral Suspension taken to prepare the *Assay preparation;*

■r_U and r_S are the sums of the peak responses of the cefuroxime axetil diasterioisomers A and B obtained from the *Assay preparation* and the *Standard preparation,* respectively;■2S (*USP27*)
and the other terms are as defined therein.

BRIEFING

Chloroprocaine Hydrochloride, *USP 26* page 422—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-5

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Chloroprocaine Hydrochloride is sterile, it meets the requirements for *Sterility* under *Chloroprocaine Hydrochloride Injection*.■2S (*USP27*)

In-Process Revision

BRIEFING

Chlorothiazide, *USP 26* page 425 and page 2950 of the *First Supplement*. See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-6

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩ —*USP Chlorothiazide RS.* ■*USP Benzothiadiazine Related Compound A RS.*■1S (*USP26*)

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Chlorpheniramine Maleate, *USP 26* page 427—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-6

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Chlorpheniramine Maleate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Chromic Chloride, *USP 26* page 447—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-7

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Cimetidine, *USP 26* page 453—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-3

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Cimetidine RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Clonidine Hydrochloride, *USP 26* page 489. It is proposed to indicate appropriate storage temperatures in the *Packaging and storage* section.

(PA5: A. Wilk) RTS—40124-7

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

In-Process Revision

BRIEFING

Clonidine Transdermal System, page 265 of *PF* 28(2) [Mar.–Apr. 2002]. It is proposed to change the wording in *Tolerances* under the *Drug release* test to better describe the rate of drug release in vitro.

(BPC: M. Marques) RTS—38682

Add the following:

■Clonidine Transdermal System

» Clonidine Transdermal System contains not less than ~~80.0 percent and not more than 120.0 percent of the labeled amount of clonidine ($C_9H_9Cl_2N_3$).2.0 mg and not more than 3.0 mg of clonidine, if labeled to deliver 0.1 mg of clonidine per day for one week; not less than 4.0 mg and not more than 6.0 mg of clonidine, if labeled to deliver 0.2 mg of clonidine per day for one week; and not less than 6.0 mg and not more than 9.0 mg of clonidine, if labeled to deliver 0.3 mg of clonidine per day for one week.~~ 80.0 percent and not more than 120.0 percent of the labeled amount of clonidine ($C_9H_9Cl_2N_3$).

Packaging and storage—Preserve in sealed, single-dose containers at a temperature not exceeding 30°.

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

USP Reference standards ⟨11⟩—*USP Clonidine Hydrochloride RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Uniformity of dosage units ⟨905⟩: meets the requirements.

Drug release ⟨724⟩—

Medium: 0.001 M phosphoric acid; 80 mL for systems containing 5 mg or less of clonidine; ~~160 mL~~ 200 mL for systems containing more than 5 mg of clonidine.

Time: 8, 24, 96, and 168 hours.

~~*Apparatus 7*—Proceed as directed in the chapter. [Size of sample holder to come.]~~

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

* A suitable cellulose membrane is available as Cuprophan 80M, from Membrana GmbH, Oehder Strasse 28, D-42289, Wuppertal, Germany, fax number +49 02 02 60 57 15.

mersion. At the end of each time interval, transfer the test sample to a fresh beaker containing the appropriate volume of *Medium*, weighed and pre-equilibrated to 32.0 ± 0.3°.

Determine the amount of $C_9H_9Cl_2N_3$ released by employing the following method.

~~*Solvent*—Dissolve 2.04 g of monobasic potassium phosphate and 2.88 g of 1-pentanesulfonic acid sodium 1-pentanesulfonate in 300 mL of water. Adjust with phosphoric acid to a pH of 3.5.~~

Mobile phase—~~Prepare a filtered and degassed mixture of *Solvent* and methanol (26:14). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~ Use a filtered and degassed 0.1% solution of triethylamine in a mixture of water and methanol (70:30), adjust with phosphoric acid to a pH of 6.0 ± 0.2. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

~~*Test solution*—At each of the test times, withdraw a 10-mL aliquot of the solution from each container.~~

~~*Standard solution*—Prepare a solution of USP Clonidine Hydrochloride RS in 0.001 M phosphoric acid having a known concentration of clonidine similar to that of the *Test solution.*~~

System suitability solution—Prepare a solution of USP Clonidine Hydrochloride RS in 0.001 M phosphoric acid having a known concentration of about 10 µg per mL.

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

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

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

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

$$CV/TA,$$

in which C is the concentration, µg per mL, of clonidine in the sample obtained from the standard curve; V is the volume, in mL, of the *Medium;* T is the time, in hours; and A is the area, in cm^2, of the transdermal system.

~~*Tolerances*—The amount of $C_9H_9Cl_2N_3$ released, as a percentage of the labeled amount of the dose absorbed in vivo, as µg per hour per cm^2, at the times specified conforms to *Acceptance Table 4.*~~

~~Time (hours)~~	~~Amount dissolved~~
~~8~~	~~between 28% and 68%~~
~~96~~	~~between 116% and 288%~~
~~168~~	~~between 170% and 357%~~

In-Process Revision

~~The amount of $C_9H_9Cl_2N_3$ released, as a percentage of the labeled amount of the dose absorbed in vivo, as µg per hour per cm², at the times specified conforms to *Acceptance Table 4.*~~ The release rate of $C_9H_9Cl_2N_3$ from the Transdermal System, expressed as µg per hour per cm^2 at the times specified, conforms to *Acceptance Table 4.*

~~Time (hours)~~	~~Amount dissolved (µg/h·cm²)~~
~~8~~	~~between 7.5 and 16.0~~
~~24~~	~~between 1.5 and 6.0~~
~~96~~	~~between 1.5 and 4.6~~
~~168~~	~~between 1.5 and 3.3~~

Time (hours)	Time for sampling (hours)	~~Amount dissolved~~ Release rate (µg/h/cm²)
0–8	8	between 7.5 and 16.0
8–24	24	between 1.5 and 4.6
24–96	96	between 1.5 and 4.6
96–168	168	between 1.5 and 3.3

Chromatographic purity—

Buffer solution—Dissolve 2.0 g of sodium 1-pentanesulfonate, 13.61 g of monobasic potassium phosphate, and 2 mL of triethylamine in about 1000 mL of water in a 2-liter volumetric flask, adjust with phosphoric acid to a pH of 4.0 ± 0.1, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (1:1), and, if necessary, adjust with phosphoric acid to a pH of 4.5 ± 0.1. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent 1—Dissolve 1 mL of triethylamine in about 800 mL of water in a 1-liter volumetric flask, adjust with phosphoric acid to a pH of 10.0 ± 0.1, dilute with water to volume, and mix. Transfer this solution to a 2-liter volumetric flask, dilute with acetonitrile to volume, and mix.

Diluent 2—Dissolve 1 mL of triethylamine and 4.36 g of dibasic potassium phosphate in about 800 mL of water in a 1-liter volumetric flask, adjust with phosphoric acid to a pH of 10.0 ± 0.1, dilute with water to volume, and mix. Transfer this solution to a 2-liter volumetric flask, dilute with acetonitrile to volume, and mix.

Standard solution—Dissolve an accurately weighed quantity of USP Clonidine Hydrochloride RS in *Diluent 1* to obtain a solution having a known concentration of about 0.1 mg per mL. Dilute an accurately measured volume of this solution quantitatively with *Diluent 2* to obtain a solution having a known concentration of about 16.2 µg of USP Clonidine Hydrochloride RS per mL (equivalent to about 14.0 µg of clonidine per mL).

Test solution—Carefully peel the release liner from each Transdermal System, and place a number of Transdermal Systems, equivalent to about 15 mg of clonidine, into a 150-mL polytef-lined screw-cap tube. Add 30 mL of *n*-heptane, cap, and mix on a vortex mixer for 2 minutes. Allow to stand for about 3 hours, but every 30 minutes during this period mix on a vortex mixer until the Transdermal Systems are delaminated. Add 0.3 mL of methanol and 45 mL of 0.01 N sulfuric acid, shake for at least 2 minutes, and centrifuge. Retain the *n*-heptane layer, and transfer the aqueous supernatant layer to a second 150-mL polytef-lined screw-cap tube. Add 9 mL of ammonium hydroxide to the aqueous supernatant layer, and mix. Extract the *n*-heptane layer with an additional 45 mL of 0.01 N sulfuric acid for at least 2 minutes, and combine this aqueous supernatant layer with the first aqueous layer in the 150-mL polytef-lined screw-

cap tube. [NOTE—The total length of time of extraction with 0.01 N sulfuric acid should not exceed 1 hour to avoid degradation of any related impurity that may be present.] Extract the aqueous layer by shaking vigorously for 2 minutes with each of two 30-mL portions of chloroform, collecting the chloroform extracts in a 150-mL polytef-lined screw-cap tube. Evaporate the chloroform extracts under nitrogen to dryness, and dissolve the residue in 15.0 mL of *Diluent 2.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains packing L10. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 4000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the Transdermal Systems taken by the formula:

$$(230.10/266.56)(1.5C/NL)(r_U/r_S),$$

in which 230.10 and 266.56 are the molecular weights of clonidine and clonidine hydrochloride, respectively; C is the concentration, in µg per mL, of USP Clonidine Hydrochloride RS in the *Standard solution; N* is the number of Transdermal Systems taken to prepare the *Test solution; L* is the labeled amount, in mg, of clonidine in each Transdermal System taken; r_U is the peak response for each impurity obtained from the *Test solution;* and r_S is the clonidine peak response obtained from the *Standard solution:* ~~not more than 1.4% of total impurities is found.~~ not more than 1.4% of any impurity is found, and not more than 2.4% of total impurities is found.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of sodium 1-pentanesulfonate and methanol (63:36). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Clonidine Hydrochloride RS in 0.01 N sulfuric acid, and dilute quantitatively, and stepwise if necessary, with 0.01 N sulfuric acid to obtain a solution having a known concentration of about ~~46 µg per mL.~~ 0.046T per mL (equivalent to about 0.040T of clonidine per mL), T being the total amount, in mg, of clonidine in each Transdermal System.

Assay preparation—Carefully peel the release liner from 1 Transdermal System, and cut the Transdermal System into segments. Quantitatively transfer the segments into an appropriate polytef-lined screw-cap centrifuge tube, add 10 mL of 0.01 N sulfuric acid saturated with *n*-heptane, accurately measured, cap, and heat to 60° for 3 hours. Add 10 mL of *n*-heptane, cap, shake vigorously for 1 minute, and heat to 60° for about 16 hours. Allow the solution to cool to room temperature, add 15 mL of 0.01 N sulfuric acid saturated with *n*-heptane, cap, and mix in a vortex mixer for about 2 minutes. Allow to separate, and filter the aqueous layer. [NOTE—If backing membrane has not delaminated, repeat with a new Transdermal System.] Use the aqueous layer as the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector, a 3.9-mm × 2-cm guard column that contains packing L2, and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation*, and record the peak re-

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sponses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of clonidine ($C_9H_9Cl_2N_3$) in the Transdermal System taken by the formula:

~~$21.58C(r_U/r_S)$,~~

$$(230.10/266.56)(25C)(r_U/r_S),$$

in which 230.10 and 266.56 are the molecular weights of clonidine and clonidine hydrochloride, respectively; *C* is the concentration, in µg per mL, of USP Clonidine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

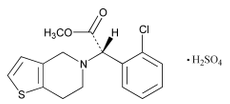
BRIEFING

Clopidogrel Bisulfate. Because there is no existing *USP* monograph for this drug substance, a new monograph is being proposed. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with a 4.6-mm × 15-cm Ultron ES-OVM brand of 5-µm column that contains packing L## (see *Chromatography* ⟨621⟩). The typical retention time for clopidogrel is about 4.6 minutes.

(PA5: A. Wilk) RTS—40048-1

Add the following:

■Clopidogrel Bisulfate



$C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ 419.90

Thieno[3,2-*c*]pyridine-5(4*H*)-acetic acid, α-(2-chlorophenyl)-6,7-dihydro-, methyl ester, (*S*)-, sulfate (1:1).

Methyl (+)-(*S*)-α-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2-*c*]pyridine-5(4*H*)-acetate, sulfate (1:1) [*120202-66-6*].

» Clopidogrel Bisulfate contains not less than 97.0 percent and not more than 101.5 percent of $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Clopidogrel Bisulfate RS. USP Clopidogrel Related Compound A RS. USP Clopidogrel Related Compound B RS. USP Clopidogrel Related Compound C RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

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C: It responds to the test for *Sulfate* ⟨191⟩.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Related compounds—

Phosphate buffer, Mobile phase, Standard stock solution, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Clopidogrel Related Compound A RS, USP Clopidogrel Related Compound B RS, and USP Clopidogrel Related Compound C RS in methanol, and dilute with methanol to obtain a solution having concentrations of about 0.1, 0.4, and 0.3 mg per mL, respectively. Dilute this solution with *Mobile phase,* and mix to obtain a solution having final concentrations of about 10, 40, and 30 µg per mL, respectively.

Test solution—Transfer about 100 mg of Clopidogrel Bisulfate, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the percentage of related compounds in the portion of Clopidogrel Bisulfate taken by the formula:

$$100(C_S / C_T)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of relevant USP Clopidogrel Related Compound RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Clopidogrel Bisulfate in the *Test solution;* r_U is the peak response for clopidogrel related compound obtained from the *Test solution;* and r_S is the peak response for relevant clopidogrel related compound obtained from the *Standard solution:* not more than 0.2% of clopidogrel related compound A is found, not more than 0.3% of clopidogrel related compound B is found, not more than 1.0% of clopidogrel related compound C is found, not more than 0.1% of any other impurity is found, and not more than 1.5% of total impurities is found.

Assay—

Phosphate buffer—Dissolve 1.36 g of monobasic potassium phosphate in about 500 mL of water, and dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (75:25). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Transfer about 100 mg of USP Clopidogrel Bisulfate RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with methanol to volume, and mix.

Standard preparation—Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

System suitability solution—Dissolve an accurately weighed quantity of USP Clopidogrel Related Compound B RS in methanol, and mix with a suitable portion of *Standard stock solution,* to obtain concentrations of about 1.0 and 0.5 mg per mL, respectively. Dilute this solution with *Mobile phase,* and mix to obtain a solution having a final concentration of about 0.05 mg per mL of clopidogrel bisulfate and about 0.1 mg per mL of clopidogrel related compound B.

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Assay preparation—Transfer about 100 mg of Clopidogrel Bisulfate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Pipet 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains packing L## (see *Chromatography* ⟨621⟩). The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 and 1.2 for enantiomers of clopidogrel related compound B, respectively, and 1.0 for clopidogrel; and the resolution, *R,* between clopidogrel and the first enantiomer of clopidogrel related compound B is not less than 2.5. Chromatograph the *Standard preparation:* the relative standard deviation for replicate injections determined from clopidogrel bisulfate is not more than 1.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the quantity, in mg, of $C_{16}H_{16}ClNO_2S \cdot H_2SO_4$ in the portion of Clopidogrel taken by the formula:

$$1000C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Clopidogrel Bisulfate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Cortisone Acetate, *USP 26* page 517—See briefing under *Alprostadil.*

(PA1: C. Anthony; PSD: C. Okeke) RTS—40156-3

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements**—Where the label states that Cortisone Acetate is sterile, it meets the requirements for *Sterility* under *Cortisone Acetate Injectable Suspension.*■2S (*USP27*)

BRIEFING

Cupric Sulfate, *USP 26* page 524—See briefing under *Acyclovir.*

(PA7b: B. Davani; PSD: C. Okeke) RTS—40204-4

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

In-Process Revision

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Deferoxamine Mesylate, *USP 26* page 546—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-5

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Deslanoside, *USP 26* page 553—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-8

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Deslanoside is sterile, it meets the requirements for *Sterility* under *Deslanoside Injection*.■2S (*USP27*)

BRIEFING

Desogestrel and Ethinyl Estradiol Tablets, page 1394 of *PF* 28(5) [Sept.–Oct. 2002]. It is proposed to specify the purity of the sodium lauryl sulfate used to prepare the *Dissolution Medium* in the *Dissolution* test.

(BPC: M. Marques) RTS—38623-1; 35216-4

Add the following:

■Desogestrel and Ethinyl Estradiol Tablets

» Desogestrel and Ethinyl Estradiol Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of desogestrel ($C_{22}H_{30}O$) and ethinyl estradiol ($C_{20}H_{24}O_2$).

Packaging and storage—Preserve in well-closed containers.

USP Reference standards ⟨11⟩—*USP Desogestrel RS.* ~~*USP Desogestrel Related Compound B RS. USP Desogestrel Related Compound C RS.*~~ *USP Ethinyl Estradiol RS.* ~~*USP Ethinyl Estradiol Related Compound A RS.*~~

Thin-layer chromatographic identification test ⟨201⟩—

~~*Adsorbent:* octadecylsilanized chromatographic silica gel mixture.~~

~~*Test solution*—Transfer a quantity of finely ground Tablets, equivalent to about 2.4 mg of desogestrel, to a stoppered 10-mL centrifuge tube, add 4.8 mL of acetone, and shake vigorously for 1 minute. Centrifuge for 5 minutes, and transfer 2.7 mL of the clear supernatant into a suitable container, protected from light. Evaporate to dryness in a hood using nitrogen at room temperature, and dissolve the residue so obtained in 0.45 mL of methylene chloride. 0.25 mL of a mixture of hexanes, methanol, and isopropyl alcohol (90:15:5).~~

~~*Standard solutions*—Prepare separate solutions in methylene chloride, a mixture of hexanes, methanol, and isopropyl alcohol (90:15:5) to contain about 2–3 mg of USP Desogestrel RS per mL and 0.5–0.6 mg of USP Ethinyl Estradiol RS per mL.~~

~~*Application volume:* 1–10 µL.~~

~~*Developing solvent system:* a mixture of toluene and ethyl acetate (80:20).~~

~~*Procedure*—Proceed as directed in the chapter. Spray the plate with a solution of sulfuric acid in alcohol (1 in 50), and dry at 110° for 5 to 10 minutes. Visualize the spots under long-wavelength UV light: ethinyl estradiol and desogestrel exhibit R_F values of about 0.30 and 0.58, respectively.~~

Test solution—Transfer 25 Tablets to a suitable container, add 50 mL of water, and sonicate until the Tablets disintegrate (if necessary, remove any coating with water before sonication). Place the sample in a separatory funnel, add 25 mL of ether, and shake well to extract the actives. Using a glass pipet, transfer the ether layer to a clean beaker, and evaporate to about 10 mL.

Standard solution—Dissolve a quantity of USP Desogestrel RS and USP Ethinyl Estradiol RS in methanol to obtain a solution containing about 0.15 mg per mL and 0.03 mg per mL, respectively.

Application volume: 30 µL.

Developing solvent system: a mixture of chloroform and alcohol (96:4).

Procedure—Proceed as directed in the chapter, and then air-dry. Spray the plate with a mixture of methanol and sulfuric acid (50:50), place in an oven at 105° for about five minutes, and examine the plate: meets the requirements.

Dissolution ⟨711⟩—

Medium: 0.05% ~~sodium lauryl sulfate dodecyl sodium sulfate~~ sodium lauryl sulfate with an assay content of not less than 95%; 500 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Determine the amounts of desogestrel ($C_{22}H_{30}O$) and ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved by employing the following method.

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~~*Diluent, Solution A, Solution B,* and *Mobile phase*—Proceed as directed in the *Assay.*~~

~~*Standard solution*—Dissolve accurately weighed quantities of USP Desogestrel RS and USP Ethinyl Estradiol RS, and dilute quantitatively, and stepwise if necessary, with *Dissolution Medium* to obtain a solution having known concentrations equivalent to the expected concentrations of the solution under test. [NOTE—A volume of acetonitrile *Diluent* not exceeding 6% of the final total volume of the *Standard solution* may be used to dissolve USP Desogestrel RS, and a volume of a mixture of methanol and water (90:10) *Diluent* not exceeding 4% of the final total volume of the *Standard solution* may be used to dissolve USP Ethinyl Estradiol RS.]~~

~~*Chromatographic system*—Proceed as directed in the *Assay.* To evaluate the system suitability requirements, use the *Standard preparation* prepared as directed in the *Assay.*~~

~~*Procedure*—Separately inject equal volumes (about 200 µL) of the *Standard solution* and a filtered centrifuged portion of the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantities of desogestrel ($C_{22}H_{30}O$) and ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved by comparison with the corresponding peak responses obtained from the *Standard solution* and the solution under test.~~

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50:50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Desogestrel standard stock solution—Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.25 mg per mL.

Ethinyl estradiol standard stock solution—Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.25 mg per mL.

Desogestrel intermediate standard solution—Transfer 1.0 mL of *Desogestrel standard stock solution* to a 50-mL volumetric flask. Dilute with *Dissolution Medium* to volume, and mix. This solution contains about 0.005 mg per mL of USP Desogestrel RS.

Ethinyl estradiol intermediate standard solution—Transfer 1.0 mL of *Ethinyl estradiol standard stock solution* to a 50-mL volumetric flask. Dilute with *Dissolution Medium* to volume, and mix. This solution contains about 0.005 mg per mL of USP Ethinyl Estradiol RS.

Standard preparation—Dilute quantitative portions of *Desogestrel intermediate standard solution* and *Ethinyl estradiol intermediate standard solution* with *Dissolution Medium* to obtain a solution containing about 0.3 µg per mL and 0.06 µg per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Test preparation—Centrifuge a portion of the dissolution sample, and use the clear supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector (for desogestrel analysis), a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of 285 nm and an emission wavelength of 310 nm; a 4.6-mm × 15-cm column that contains packing L11; and a 4.6-mm × 12.5-mm guard column that also contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention

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times are about 0.2 for ethinyl estradiol and 1.0 for desogestrel, and the relative standard deviation is not more than 3.0%.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{22}H_{30}O$ and $C_{20}H_{24}O_2$ dissolved by the formula:

$$(0.05C)(100/K)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Desogestrel RS or USP Ethinyl Estradiol RS in the *Standard preparation; K* is the labeled amount, in mg per Tablet, of $C_{22}H_{30}O$ or $C_{20}H_{24}O_2$; and r_U and r_S are the peak responses obtained for desogestrel or ethinyl estradiol from the *Test preparation* and the *Standard preparation,* respectively.

Tolerances—Not less than 80% *(Q)* of each of the labeled amounts of $C_{22}H_{30}O$ and $C_{20}H_{24}O_2$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements for *Content Uniformity* with respect to desogestrel and to ethinyl estradiol.

Loss on drying ⟨731⟩—Powder ~~20-40~~ 40 Tablets, and dry the portion at 105° for 3 hours: it loses not more than 4.0% of its weight.

Water, *Method Ic* ⟨921⟩: ~~not more than 5.4%, using 35 mg of ground Tablets heated at 170°.~~ not more than 5.4% using a portion of the Tablet of about 35 mg and a suitable evaporation technique that releases the water by heating the specimen in a stream of dry inert gas, this gas then being passed into the cell.

Related compounds—

~~*Diluent, Solution A, Solution B, Mobile phase, Desogestrel standard stock solution,* and *Ethinyl estradiol standard stock solution*—Prepare as directed in the *Assay.*~~

~~*Related compounds standard stock solution*—Separately dissolve accurately weighed quantities of USP Ethinyl Estradiol Related Compound A RS, USP Desogestrel Related Compound B RS, and USP Desogestrel Related Compound C RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentrations of about 0.006 mg per mL, 0.00375 mg per mL, and 0.00375 mg per mL, respectively. concentration of about 50% relative to the expected concentration of ethinyl estradiol and desogestrel in the *Test solution.*~~

~~*Standard solution*—Transfer 5.0 mL of *Ethinyl estradiol standard stock solution* and 2.0 mL of *Related compounds standard stock solution* to a 100 mL volumetric flask, add an accurately measured volume of *Desogestrel standard stock solution* to obtain a final solution having a concentration, in mg per mL, corresponding to the expected concentration of desogestrel in the *Test solution.* Dilute with *Diluent* to volume, and mix. Transfer 2.0 mL of *Related compounds standard stock solution* and an accurately measured volume each of *Ethinyl estradiol standard stock solution* and *Desogestrel standard stock solution* to a 100 mL volumetric flask to obtain a final solution having an accurately known concentration in mg per mL, corresponding approximately to the expected concentration of desogestrel and ethinyl estradiol in the *Test solution.* Dilute with *Diluent* to volume, and mix.~~

~~*Test solution*—Use the *Assay preparation.*~~

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~~*Chromatographic system*~~—~~Prepare as directed in the *Assay*. [NOTE—The related compounds A and C Ethinyl estradiol related compound A and desogestrel related compound C are monitored using a wavelength of 230 250 nm, and all other compounds are monitored at 210 205 nm.] Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the column efficiency determined from the ethinyl estradiol peak is not less than 2500 theoretical plates; the tailing factor for the ethinyl estradiol peak is between 0.9 and 1.5; and the relative standard deviation for replicate injections determined from the desogestrel and ethinyl estradiol peaks is not more than 2.0%, and not more than 5.0% determined from the peaks for each related compound.~~

~~*Procedure*—Separately inject equal volumes (about 25 200 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak heights areasresponses for ethinyl estradiol related compound A, desogestrel related compound B, and desogestrel related compound C, disregarding the peak, if any, with a retention time of about 12 minutes.Calculate the percentage of ethinyl estradiol related compound A in the portion of Tablets taken by the formula:~~

$$~~4166.6C(r_U/r_S),~~$$

$$~~200(C/L)(r_U/r_S),~~$$

~~in which *C* is the concentration, in mg per mL, of USP Ethinyl Estradiol Related Compound A RS in the *Standard solution; L* is the labeled amount, in mg, of ethinyl estradiol in each Tablet; and r_U and r_S are the peak heights areas responses for ethinyl estradiol related compound A obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% 2.0% of ethinyl estradiol related compound A is found. Calculate the percentages of desogestrel related compound B and desogestrel related compound C in the portion of Tablets taken by the formula:~~

$$~~666.6C(r_U/r_S),~~$$

$$~~200(C/L)(r_U/r_S),~~$$

~~in which *C* is the concentration, in mg per mL, of USP Desogestrel Related Compound B RS or USP Desogestrel Related Compound C RS in the *Standard solution; L* is the labeled amount, in mg, of desogestrel in each Tablet; and r_U and r_S are the peak heights areas responses for desogestrel related compound B or desogestrel related compound C, as appropriate, obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% each 2.0% of desogestrel related compound B is found; not more than 3.0% of desogestrel related compound C is found; and not more than 2.0% 5.0% of total related compounds is found.~~

Solution A—Prepare a mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50:50).

Solution B—Prepare a mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (80:20).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed under *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of acetonitrile and water (50:50).

In-Process Revision

Desogestrel standard stock solution—Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL.

Ethinyl estradiol standard stock solution—Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL.

Standard solution—Dilute quantitative portions of *Desogestrel standard stock solution* and *Ethinyl estradiol standard stock solution* with *Diluent* to obtain a solution containing about 0.6 µg per mL and 0.12 µg per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Test solution 1—Transfer 20 Tablets to a 200-mL volumetric flask. Add about 120 mL of *Diluent,* and shake for about 30 minutes. Dilute with *Diluent* to volume, and mix. Centrifuge a portion of the dissolution sample, and use the clear supernatant.

Test solution 2—Dilute a portion of *Test solution 1* with *Diluent* to obtain a solution containing about 0.6 µg per mL of ethinyl estradiol.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a programmable variable wavelength UV detector and a spectrofluorometric detector with an excitation wavelength of 285 nm and an emission wavelength of 310 nm; a 4.6-mm × 15-cm column that contains packing L11; and a 4.6-mm × 12.5-mm guard column that also contains packing L11. The chromatograph is programmed as follows: Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are 0.18 for ethinyl estradiol and 1.0 for desogestrel; the resolution, *R,* between ethinyl estradiol and desogestrel is not less than 2.0; the tailing factor is not more than 2.0 for ethinyl estradiol and desogestrel; and the relative standard deviation for replicate injections is not more than 2.0%.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution	UV Detector (nm)	Flow Rate (mL/min.)
0	100	0	equilibration	210	2
0–4	100	0	isocratic	210	2
4–10	100	0	isocratic	244	2
10–20	100	0	isocratic	210	2
20–25	0	100	linear gradient	210	2.5
25–30	0	100	isocratic	210	3
30–32	100	0	linear gradient	210	2
32–35	100	0	re-equilibration	210	2

In-Process Revision

Procedure—Inject a volume (about 200 µL) of *Test solution 2* into the chromatograph, record the chromatograms, and measure the peak heights for the major peaks obtained within 20 minutes. Calculate the percentage of 17β-ethinyl estradiol in the portion of Tablets taken by the formula:

$$100(r_U / r_S),$$

in which r_U is the height of any peak at relative retention time of 0.20; and r_S is the peak height of ethinyl estradiol obtained with the spectrofluorometric detector. Inject a volume (about 200 µL) of *Test solution 1* into the chromatograph, record the chromatograms, and measure the peak heights for the major peaks obtained within 20 minutes. Calculate the percentage of estrone in the portion of Tablets taken by the formula:

$$100(r_U / r_S) - E,$$

in which r_U is the height of any peak at relative retention time of 0.20; r_S is the peak height of ethinyl estradiol obtained with the UV detector at 210 nm; and E is the percentage of 17β-ethinyl estradiol obtained in the Tablets. Calculate the percentage of 3-ketodesogestrel in the portion of Tablets taken by the formula:

$$100(1/F)(r_U / r_S),$$

in which r_U is the height of any peak at relative retention time of 0.32 obtained with the UV detector at 244 nm; r_S is the peak height of desogestrel obtained with the UV detector at 210 nm; and F is the relative response factor, equal to 4.1. Calculate the percentage of any other impurity taken by the formula:

$$100(r_i / r_S),$$

in which r_i is the height of any peak other than those mentioned above; and r_S is the peak height of ethinyl estradiol obtained with the UV detector. Any peak below 0.1% is not considered. Not more than 0.5% of ethinyl estradiol impurities is found; not more than 0.5% of desogestrel impurities is found; and not more than 2.0% of total impurities is found.

Assay—

~~*Diluent*—Prepare a mixture of acetonitrile methanol and water (4:1). (60:40).~~

~~*Solution A*—Use acetonitrile.~~

~~*Solution B*—Prepare a filtered and degassed mixture of acetonitrile and water (1:1).~~

~~*Mobile phase*—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Desogestrel standard stock solution*—Dissolve an accurately weighed quantity of USP Desogestrel RS in *Diluent* methanol to obtain a solution having a known concentration of about 0.25 0.35 mg per mL.~~

~~*Ethinyl estradiol standard stock solution*—Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in *Diluent* methanol to obtain a solution having a known concentration of about 0.25 0.21 mg per mL.~~

~~*Standard preparation*—Transfer 5.0 mL of *Ethinyl estradiol standard stock solution* to a 100 mL volumetric flask, and add an accurately measured volume of *Desogestrel standard stock solution* to obtain a solution having a known concentration, in mg per mL, corresponding to the expected concentration of desogestrel in the *Assay preparation*. Dilute with *Diluent* to volume, and mix. Transfer an accurately measured volume each of *Ethinyl estradiol standard stock solution* and *Desogestrel standard stock solution* to a 100 mL volumetric flask to obtain a final solution having an accurately known concentration in mg per mL, corresponding approximately to the expected concentration of desogestrel and ethinyl estradiol in the *Assay preparation*. Dilute with *Diluent* to volume, and mix.~~

In-Process Revision

Assay preparation—Transfer 10 14 10 Tablets to a 30-mL 50-mL stoppered centrifuge tube, add 20.0 30 mL of *Diluent,* and sonicate for 25 minutes with intermittent mixing on a vortex mixer, until all Tablets have broken apart. Extract for 30 minutes on a benchtop shaker. Centrifuge, and use the clear supernatant. [NOTE—Retain a portion of this solution to use as the *Test solution* in the test for *Related compounds.*]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with either a programmable variable wavelength detector or two separate detectors capable of monitoring at 210 205 nm and at 230 250 230 nm and a 4.6-mm × 15-cm 25-cm column that contains stable-bonded 5-µm packing L1. The flow rate is about 2 1.5 mL per minute, and the column temperature is maintained at 40°. The chromatograph is programmed as follows. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure*: the column efficiency determined from the ethinyl estradiol peak is not less than 2500 theoretical plates; the tailing factor for the ethinyl estradiol peak is between 0.9 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0% 1.5%,determined from the desogestrel and ethinyl estradiol peaks.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–4.5 0–12.0	0	100	isocratic
4.5–4.6 12.0–12.1	0→100	100→0	linear gradient
4.6–10.7 12.1–25.0	100	0	isocratic
10.7–10.8 25.0–25.1	100→0	0→100	linear gradient
25.1–30.0	0	100	isocratic

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas at 210 205nm. Separately calculate the amounts, in µg, of desogestrel ($C_{22}H_{30}O$) and ethinyl estradiol ($C_{20}H_{24}O_2$) in the portion of Tablets taken by the formula:

$$(LC_S/C_U)(r_U/r_S),$$

in which L is the labeled quantity, in µg, of the relevant analyte in each Tablet; C_S is the concentration, in µg per mL, of the appropriate USP Reference Standard in the *Standard preparation;* C_U is the concentration, in µg per mL, of the corresponding analyte in the *Assay preparation,* based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the peak responses areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and 20 mM potassium phosphate buffer, pH 6.0 (50:50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of acetonitrile and water (50:50).

Desogestrel standard stock solution—Dissolve an accurately weighed quantity of USP Desogestrel RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL.

Ethinyl estradiol standard stock solution—Dissolve an accurately weighed quantity of USP Ethinyl Estradiol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.3 mg per mL.

In-Process Revision

Standard preparation—Dilute appropriate aliquots of *Desogestrel standard stock solution* and *Ethinyl estradiol standard stock solution* with *Diluent* to obtain a solution having a known concentration of about 0.6 µg per mL and 0.12 µg per mL of USP Desogestrel RS and USP Ethinyl Estradiol RS, respectively.

Assay preparation—Transfer 20 Tablets into a 200-mL volumetric flask. Add about 120 mL of *Diluent,* and shake for about 30 minutes. Dilute with *Diluent* to volume, and mix. Centrifuge a portion of the sample, and transfer an accurately measured volume to a 50-mL volumetric flask to obtain a final concentration of about 0.6 µg per mL of desogestrel. Dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector (for desogestrel analysis), a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of 285 nm and an emission wavelength of 310 nm; a 4.6-mm × 15-cm column that contains packing L11; and a 4.6-mm × 12.5-mm guard column that also contains packing L11. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.2 for ethinyl estradiol and 1.0 for desogestrel; the tailing factor for both analytes is not more than 2.0; and the relative standard deviation is not more than 2.0%.

Procedure—Separately inject equal volumes (about 200 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of desogestrel ($C_{22}H_{30}O$) and ethinyl estradiol ($C_{20}H_{24}O_2$) in the portion of Tablets taken by the formula:

$$(500C/V)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Desogestrel RS or USP Ethinyl Estradiol RS in the *Standard preparation; V* is the volume of the aliquot of solution taken for the *Assay preparation;* and r_U and r_S are the peak responses for desogestrel or ethinyl estradiol obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Desoxycorticosterone Acetate, *USP 26* page 556—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-4

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Desoxycorticosterone Acetate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Desoxycorticosterone Acetate is sterile, it meets the requirements of the tests for *Sterility* and *Bacterial endotoxins* under *Desoxycorticosterone Acetate Injection*. Where the label states that Desoxycorticosterone Acetate must be subjected to

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further processing during the preparation of injectable dosage forms, it meets the requirements of the test for *Bacterial endotoxins* under *Desoxycorticosterone Acetate Injection*.■2S (*USP27*)

BRIEFING

Dexamethasone Acetate, *USP 26* page 562—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-5

Change to read:
Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:
Labeling—Label it to indicate whether it is hydrous or anhydrous.

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

Change to read:
USP Reference standards ⟨11⟩—*USP Dexamethasone Acetate RS*.

■*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Dextrose, *USP 26* page 581—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-8

Change to read:
Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:
Labeling—Label it to indicate whether it is hydrous or anhydrous.

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Diazoxide, *USP 26* page 590—See briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-9

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Diazoxide RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Dibucaine Hydrochloride, *USP 26* page 593—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-9

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Dibucaine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Dicyclomine Hydrochloride, *USP 26* page 598—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-6

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

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Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dicyclomine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Dicyclomine Hydrochloride Capsules, *USP 26* page 598 and page 2953 of the *First Supplement;* **Dicyclomine Hydrochloride Injection,** *USP 26* page 599; **Dicyclomine Hydrochloride Oral Solution,** *USP 26* page 599; **Dicyclomine Hydrochloride Syrup,** *USP 26* page 600; **Dicyclomine Hydrochloride Tablets,** *USP 26* page 600. It is proposed to replace the gas chromatographic *Assay* with a stability-indicating liquid chromatographic procedure to improve the ruggedness of the method. There was also a concern that dicyclomine hydrochloride could degrade in the injection port and column due to the high temperatures during the analysis. The new *Assay* procedure is based on the analyses performed with 3.5-µm XTerra RP-8 brand of L7 column. The typical retention time for the dicyclomine peak is about 5.5 minutes.

(PA4: E. Gonikberg) RTS—39530-5

Change to read:

Assay—

~~*Internal standard solution*—Dissolve a quantity of phenacetin in methanol to obtain a solution having a concentration of about 2.5 mg per mL.~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Dicyclomine Hydrochloride RS in methanol to obtain a solution having a known concentration of about 1 mg per mL. Transfer 2.0 mL of this solution to a 10-mL volumetric flask, add 2.0 mL of *Internal standard solution,* dilute with methanol to volume, and mix.~~

~~*Assay preparation*—Remove, as completely as possible, the contents of not fewer than 20 Capsules, and mix the contents. Transfer an accurately weighed portion of the powder, equivalent to about 10 mg of dicyclomine hydrochloride, to a 25-mL volumetric flask, add 10.0 mL of *Internal standard solution,* dilute with methanol to volume, and mix. Filter 15 mL of this solution, discarding the first 5 mL, and transfer 5.0 mL to a 10-mL volumetric flask. Dilute with methanol to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 15-m × 0.5-mm fused-silica column coated with a 1-µm phase G3. The column is maintained at 160° for 2 minutes, then programmed at 20° per minute for 4 minutes, and held at a final temperature of 240° for 5 minutes. The injection port and detector temperatures are maintained at 250°. Nitrogen is used as the carrier gas at a flow rate of 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between phenacetin and dicyclomine is not less than 2; the tailing factor for dicyclomine is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 2 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of dicyclomine hydrochloride ($C_{19}H_{35}NO_2 \cdot HCl$) in the portion of Capsules taken by the formula:~~

$$~~50C(R_U / R_S),~~$$

~~in which *C* is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and R_U and R_S are the ■peak response ratios of dicyclomine to phenacetin■1S (*USP26*)~~ obtained from the *Assay preparation* and the *Standard preparation,* respectively.

■*0.02 M Phosphate buffer, pH 7.5*—Dissolve 2.72 g of monobasic potassium phosphate in 900 mL of water, adjust with 10% sodium hydroxide to a pH of 7.5 ± 0.1, dilute with water to 1000 mL, and mix.

Mobile phase—Prepare a mixture of acetonitrile and *0.02 M Phosphate buffer, pH 7.5* (70:30), filter, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of acetonitrile and water (70:30).

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Standard preparation—Dissolve an accurately weighed quantity of USP Dicyclomine Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 0.4 mg per mL. [NOTE—This solution is stable for 2 days].

Assay preparation—Remove, as completely as possible, the contents of not less than 20 Capsules, and mix the contents. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of dicyclomine hydrochloride, to a 50-mL volumetric flask. Add 2.0 mL of water, and sonicate for at least 2 minutes to disperse the sample. Add 35 mL of acetonitrile, sonicate for at least 5 minutes, and shake on a mechanical shaker for at least 30 minutes. Add 10 mL of water, allow the preparation to equilibrate to room temperature, then dilute with water to volume, and mix. Centrifuge, for at least 5 minutes, a portion of this solution in a 15-mL glass centrifuge tube. Use the clear supernatant.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 15-cm column containing 3-µm packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the responses as directed for *Procedure:* the tailing factor for the analyte peak is not more than 1.5, and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Capsules taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the areas of the dicyclomine peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Dicyclomine Hydrochloride Injection, *USP 26* page 599. It was reported that the current *Assay* method did not work as written due to sample preparation and extraction issues. On the basis of comments received, it is proposed to replace the gas chromatographic *Assay* with a stability-indicating liquid chromatographic procedure. See also briefing under *Dicyclomine Hydrochloride Capsules*.

(PA4: E. Gonikberg) RTS—39530-3

Change to read:

Assay—

~~*Internal standard solution, Standard preparation,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules.*~~

~~*Assay preparation*—Transfer an accurately measured volume of Injection, equivalent to 5.0 mg of dicyclomine hydrochloride, to a solid-phase extraction cartridge. Elute with 4 mL of chloroform and then elute with three 2-mL portions of chloroform, collecting the eluates in a 25-mL volumetric flask. Add 5.0 mL of *Internal standard solution,* dilute with methanol to volume, and mix.~~

~~*Procedure*—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Injection taken by the formula:~~

~~$$25C(R_U / R_S),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation,* and the other terms are as defined therein.~~

■*0.02 M Phosphate buffer, pH 7.5, Mobile phase, Diluent, Standard preparation,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*.

In-Process Revision

Assay preparation—Prepare a composite sample of at least 5 ampules or 2 vials. Transfer an accurately measured volume of the composite sample, equivalent to 20.0 mg of dicyclomine hydrochloride, into a 50-mL volumetric flask, and dilute with *Diluent* to volume.

Procedure—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Injection taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and the other terms are as defined therein.■2S (*USP27*)

BRIEFING

Dicyclomine Hydrochloride Oral Solution, *USP 26* page 599. It was reported that the current *Assay* method did not work as written due to sample preparation and extraction issues. On the basis of comments received, it is proposed to replace the gas chromatographic *Assay* with a stability-indicating liquid chromatographic procedure. See also briefing under *Dicyclomine Hydrochloride Capsules*.

(PA4: E. Gonikberg) RTS—39530-2

Change to read:

Assay—

~~*Internal standard solution, Standard preparation,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules.*~~

~~*Assay preparation*—Transfer an accurately measured volume of Oral Solution, equivalent to 5.0 mg of dicyclomine hydrochloride, to a solid-phase extraction cartridge. Elute with 4 mL of chloroform and then elute with three 2-mL portions of chloroform, collecting the eluates in a 25-mL volumetric flask. Add 5.0 mL of *Internal standard solution,* dilute with methanol to volume, and mix.~~

~~*Procedure*—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of dicyclomine hydrochloride ($C_{19}H_{35}NO_2 \cdot HCl$) in the portion of Oral Solution taken by the formula:~~

~~$$25C(R_U / R_S),$$~~

~~in which C is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and the other terms are as defined therein.~~

■*0.02 M Phosphate buffer, pH 7.5, Mobile phase,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*.

Diluent—Prepare a mixture of *0.02 M Phosphate buffer, pH 7.5* and acetonitrile (65:35).

Standard preparation—Dissolve an accurately weighed quantity of USP Dicyclomine Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL. [NOTE—This solution is stable for 2 days.]

Assay preparation—Using a "to contain" pipet, transfer an accurately measured volume of Oral Solution, equivalent to 10.0 mg of dicyclomine hydrochloride, to a 100-mL volumetric flask. Rinse the pipet with several small portions of *Diluent*, adding the rinsings to the volumetric flask. Dilute with *Diluent* to volume, and mix.

Procedure—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Oral Solution taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and the other terms are as defined therein.■2S (*USP27*)

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BRIEFING

Dicyclomine Hydrochloride Syrup, *USP 26* page 600. It was reported that the current *Assay* method did not work as written due to sample preparation and extraction issues. On the basis of comments received, it is proposed to replace the gas chromatographic *Assay* with a stability-indicating liquid chromatographic procedure. See also briefing under *Dicyclomine Hydrochloride Capsules*.

(PA4: E. Gonikberg) RTS—39530-2

Change to read:

Assay—

~~*Internal standard solution, Standard preparation,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*.~~

~~*Assay preparation*—Transfer an accurately measured volume of Syrup, equivalent to 5.0 mg of dicyclomine hydrochloride, to a solid-phase extraction cartridge. Elute with 4 mL of chloroform and then elute with three 2-mL portions of chloroform, collecting the eluates in a 25-mL volumetric flask. Add 5.0 mL of *Internal standard solution,* dilute with methanol to volume, and mix.~~

~~*Procedure*—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Syrup taken by the formula:~~

~~$$25C(R_U / R_S),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and the other terms are as defined therein.~~

■*0.02 M Phosphate buffer, pH 7.5, Mobile phase,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*.

Diluent—Prepare a mixture of *0.02 M Phosphate buffer, pH 7.5* and acetonitrile (65:35).

Standard preparation—Dissolve an accurately weighed quantity of USP Dicyclomine Hydrochloride RS in *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL. [NOTE—This solution is stable for 2 days.]

Assay preparation—Using a "to contain" pipet, transfer an accurately measured volume of Syrup, equivalent to 10.0 mg of dicyclomine hydrochloride, to a 100-mL volumetric flask. Rinse the pipet with several small portions of *Diluent*, adding the rinsings to the volumetric flask. Dilute with *Diluent* to volume, and mix.

Procedure—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Syrup taken by the formula:

$$100C(r_U / r_S),$$

in which *C* is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and the other terms are as defined therein. ■2S (*USP27*)

BRIEFING

Dicyclomine Hydrochloride Tablets, *USP 26* page 600—See briefing under *Dicyclomine Hydrochloride Capsules*.

(PA4: E. Gonikberg) RTS—39530-4

Change to read:

Assay—

~~*Internal standard solution, Standard preparation,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*.~~

~~*Assay preparation*—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of dicyclomine hydrochloride, to a 50-mL volumetric flask, add 20.0 mL of *Internal standard solution,* dilute with methanol to volume, and mix. Filter 15 mL of this solution, discarding the first 5 mL, and transfer 5.0 mL to a 10-mL volumetric flask. Dilute with methanol to volume, and mix.~~

~~*Procedure*—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Tablets taken by the formula:~~

~~$$100C(R_U / R_S),$$~~

~~in which *C* is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation,* and the other terms are as defined therein.~~

■*0.02 M Phosphate buffer, pH 7.5, Mobile phase, Diluent, Standard preparation,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*.

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Assay preparation—Transfer not fewer than 20 Tablets to a tared container, and determine the average Tablet weight. Grind the Tablets to a fine powder using a glass mortar and pestle. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of dicyclomine hydrochloride, to a 50-mL volumetric flask. Proceed as directed under *Dicyclomine Hydrochloride Capsules* beginning with "Add 2.0 mL of water."

Procedure—Proceed as directed in the *Assay* under *Dicyclomine Hydrochloride Capsules*. Calculate the quantity, in mg, of $C_{19}H_{35}NO_2 \cdot HCl$ in the portion of Tablets taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Dicyclomine Hydrochloride RS in the *Standard preparation;* and the other terms are as defined therein.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Diethylstilbestrol RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Diethylstilbestrol, *USP 26* page 604—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-6

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Dihydroergotamine Mesylate, *USP 26* page 617. It is proposed to update the monograph replacing the TLC related alkaloids and UV-VIS assay tests with an HPLC method. *Identification* test *C* is changed accordingly as well. This method was validated with a Hypersil ODS brand of L1 packing. The typical retention time for dihydroergotamine mesylate is about 12.5 minutes.

(PA3: S. Salado) RTS—39766-1

Change to read:

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 50 µg per mL.

Medium: 70% alcohol. Absorptivities at 280 nm, calculated on the dried basis, do not differ by more than 3.0%.

C: ~~The principal spot from the *Test preparation* found in the test for *Related alkaloids* corresponds in R_f value to that obtained from the *Standard preparation*.~~

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■The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*■2S (*USP27*)

Delete the following:

■~~**Related alkaloids—**~~

~~*Solvent mixture*—Mix 10 volumes of chloroform, 10 volumes of methanol, and 1 volume of ammonium hydroxide.~~

~~*Test preparation*—Prepare a solution of Dihydroergotamine Mesylate in *Solvent mixture* to contain 20 mg per mL.~~

~~*Standard preparation* and *Standard dilutions*—Prepare a solution of USP Dihydroergotamine Mesylate RS in *Solvent mixture* to contain 20 mg per mL *(Standard preparation).* Prepare a series of dilutions of *Standard preparation* in *Solvent mixture* to contain 0.40 mg, 0.20 mg, and 0.10 mg per mL *(Standard dilutions).*~~

~~*Procedure*—In a suitable chromatographic chamber arranged for thin-layer chromatography place a volume of a solvent system consisting of a mixture of chloroform and alcohol (9:1) sufficient to develop the chromatogram, cover, and allow to equilibrate for 30 minutes. Apply 5-µL portions of *Test preparation, Standard preparation,* and each of the three *Standard dilutions* to a suitable thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel. Allow the spots to dry, and develop the chromatogram until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a solution prepared by dissolving 800 mg of *p*-dimethylaminobenzaldehyde in a cooled mixture of 80 g of alcohol and 20 g of sulfuric acid. The R_f value of the principal spot obtained from the *Test preparation* corresponds to that obtained from the *Standard preparation.* Estimate the concentration of any other spots observed in the lane for the *Test preparation* by comparison with the *Standard dilutions.* The spots from the 0.40-, 0.20-, and 0.10-mg-per-mL dilutions are equivalent to 2.0%, 1.0%, and 0.50% of impurities, respectively. The sum of the impurities is not greater than 2.0%.~~■2S (*USP27*)

Add the following:

■**Chromatographic purity—**

Diluent 1, Diluent 2, Solution A, Solution B, and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution 1— Use the *Standard preparation* prepared as directed in the *Assay.*

Standard solution 2—Dilute a known volume of *Standard solution 1* with *Diluent 2* and stepwise if necessary with *Diluent 2* to obtain a solution containing about 0.3 µg per mL.

Test solution—Use the *Assay preparation* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.0-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	60	40	equilibration
0–12	60–50	40–50	linear gradient
12–20	50–15	50–85	linear gradient
20–25	15	85	isocratic
24–25	15–60	85–40	linear gradient
25–31	60	40	re-equilibration

Chromatograph 10 µL of *Standard solution 1,* and record the peak areas as directed for *Procedure:* the tailing factor is between 0.8 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Standard solution 2,* and record the peak areas as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

Procedure—Separately inject equal volumes (about 30 µL) of the *Standard solution 2* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the analyte peaks. Calculate the percentage of each impurity in the portion of Dihydroergotamine Mesylate taken by the formula:

$$5000\ (C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Dihydroergotamine Mesylate RS in the *Standard solution 2; W* is the weight, in mg, of Dihydroergotamine Mesylate taken to prepare the *Test solution;* r_i is the peak area of each im-

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purity obtained from the *Test solution;* and r_S is the peak area of dihydroergotamine mesylate obtained from the *Standard solution 2:* not more than 0.5% of one individual impurity is found; not more than 1.0% of total impurities is found. ■2S (*USP27*)

Change to read:

Assay—

~~*Standard preparation*—Transfer about 10 mg of USP Dihydroergotamine Mesylate RS, accurately weighed, to a 200-mL volumetric flask, add 2 mL of methanol, dilute with tartaric acid solution (1 in 100) to volume, and mix.~~

~~*Assay preparation*—Using about 10 mg of Dihydroergotamine Mesylate, accurately weighed, prepare as directed for *Standard preparation.*~~

~~*Procedure*—Transfer 3.0 mL each of the *Standard preparation,* the *Assay preparation,* and tartaric acid solution (1 in 100) to provide the blank, to separate conical flasks. Add 6.0 mL of *p*-dimethylaminobenzaldehyde TS to each, shake, and allow to stand for 20 minutes. Concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 585 nm, with a suitable spectrophotometer, against the blank. Calculate the quantity, in mg, of $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ in the portion of Dihydroergotamine Mesylate taken by the formula:~~

~~$$0.2C(A_U/A_S),$$~~

~~in which C is the concentration, in µg per mL, of USP Dihydroergotamine Mesylate RS in the *Standard preparation,* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively.~~

■*Diluent 1*—Prepare a solution of 0.1 mL of phosphoric acid in 1000 mL of water.

Diluent 2—Prepare a mixture of *Diluent 1* and acetonitrile (60:40).

Solution A—Prepare a filtered and degassed mixture of water, 25 percent ammonia water, and 98% formic acid (1000:10:5). Adjust the pH to 8.50.

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Solution A* (80:20).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments to either solution as necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Dihydroergotamine Mesylate RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with *Diluent 1* to obtain a solution having a known concentration of about 0.6 mg per mL. [NOTE—The final ratio of acetonitrile and *Diluent 1* should be similar to the final ratio obtained in the *Assay preparation.*]

Assay preparation—Transfer about 30 mg of Dihydroergotamine Mesylate, accurately weighed, to a 50-mL volumetric flask, dissolve with 20 mL of acetonitrile, dilute with *Diluent* 1 to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and 4.0-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	60	40	equilibration
0–12	60–50	40–50	linear gradient
12–20	50–15	50–85	linear gradient
20–25	15	85	isocratic
24–25	15–60	85–40	linear gradient
25–31	60	40	re-equilibration

Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the tailing factor is between 0.8 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

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measure the areas for the analyte peaks. Calculate the quantity, in mg, of $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ in the portion of Dihydroergotamine Mesylate taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Dihydroergotamine Mesylate RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Dimenhydrinate, *USP 26* page 628—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-7

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Dimenhydrinate is sterile, it meets the requirements for *Sterility* under *Dimenhydrinate Injection.*■2S (*USP27*)

BRIEFING

Dimercaprol, *USP 26* page 631—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-8

Change to read:

Packaging and storage—Preserve in tight containers.

■Store■2S (*USP27*) in a cold place.

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Dimercaprol is sterile, it meets the requirements for *Sterility* under *Dimercaprol Injection.*■2S (*USP27*)

BRIEFING

Diphenhydramine Hydrochloride, *USP 26* page 637—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-10

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

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Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Diphenhydramine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Dipyridamole, *USP 26* page 644 and page 2956 of the *First Supplement*—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-10

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dipyridamole RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Dobutamine Hydrochloride, *USP 26* page 651—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-11

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dobutamine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

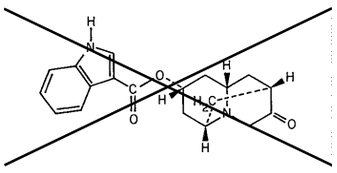
Add the following:

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

BRIEFING

Dolasetron Mesylate, *USP 26* page 658 and page 1025 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-9



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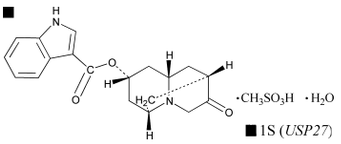

■1S (*USP27*)

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dolasetron Mesylate RS. USP Dolasetron Mesylate Related Compound A RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Change to read:

Related compounds—

0.01 M Dibasic ammonium phosphate solution—Dissolve 132.1 g of dibasic ammonium phosphate in 1000 mL of water. Dilute 10.0 mL of this solution with about 990 mL of water, adjust with 2.0 M phosphoric acid to a pH of 7.0, and mix.

Diluent—Prepare a mixture of water and acetonitrile (4:1).

Solution A—Prepare a filtered and degassed mixture of *0.01 M Dibasic ammonium phosphate solution* and acetonitrile (1000:53).

Solution B—Prepare a filtered and degassed mixture of acetronitrile and *0.01 M Dibasic ammonium phosphate solution* (795:295).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution of indole and USP Dolasetron Mesylate RS in *Diluent* having known concentrations of about 0.004 mg per mL and 0.03 mg per mL, respectively.

Standard solution 1—Dissolve an accurately weighed quantity of USP Dolasetron Mesylate RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.03 mg per mL.

Standard solution 2—Dissolve accurately weighed quantities of USP Dolasetron Mesylate RS and USP Dolasetron Mesylate Related Compound A RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 6 mg per mL and 0.0072 mg per mL, respectively.

Test solution—Transfer about 150 mg of Dolasetron Mesylate, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–28	100→0	→100	linear gradient
28–38	250	100	isocratic
38–40	0→100	100→0	linear gradient
40–50	100	0	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the first eluting peak, indole, and the second eluting peak, dolasetron mesylate, is not less than 1.5.

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■[NOTE—If the dolasetron mesylate peak is found to elute before the indole peak, condition the column as follows. Fill up the column with *Solution A*, plug the column, and place the column in a convection oven at 105° for about 16 hours. Retest the column.]■1S (*USP27*)
Chromatograph *Standard solution 1,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution 1, Standard solution 2 ,* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of dolasetron mesylate related compound A in the portion of Dolasetron Mesylate taken by the formula:

~~(181.2/217.8)1000(r_U/r_S),~~

■2500(181.2/217.8)(C_{RC}/W)(r_U/r_S),■1S (*USP27*)

in which 181.2 and 217.8 are the molecular weights of dolasetron mesylate related compound A base and dolasetron mesylate related compound A hydrochloride, respectively;

■C_{RC} is the concentration, in mg per mL, of USP Dolasetron Mesylate Related Compound A RS in *Standard solution 2; W* is the weight, in mg, of Dolasetron Mesylate taken to prepare the *Test solution;* ■1S (*USP27*)
and r_U and r_S are the peak areas for dolasetron mesylate related compound A obtained from the *Test solution* and *Standard solution 2,* respectively: not more than 0.1% of dolasetron mesylate related compound A is found. Calculate the percentage of each impurity (other than dolasetron mesylate related compound A) in the portion of Dolasetron Mesylate taken by the formula:

~~200(r_i/r_S),~~

■2500(C/W)(r_i/r_S),■1S (*USP27*)

in which

■C is the concentration, in mg per mL, of USP Dolasetron Mesylate RS in *Standard solution 1; W* is as defined above;■1S (*USP27*)
r_i is the peak area for each impurity obtained from the *Test solution;* and r_S is the peak area for dolasetron mesylate obtained from *Standard solution 1:* not more than 0.1% of any individual impurity is found; and not more than 0.3% of total impurities is found.

Add the following:

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

BRIEFING

Dopamine Hydrochloride, *USP 26* page 659—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-12

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dopamine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

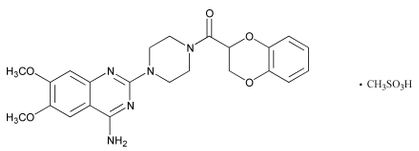
BRIEFING

Doxazosin Mesylate, page 61 of *PF* 29(1) [Jan.–Feb. 2003]. On the basis of comments received, it is proposed to revise the *Procedure* in the test for *Chromatographic purity* to change the relative standard deviation for replicate injections to 2.0% and to change the limit for any other individual impurity to 0.25%. It is also proposed to add storage conditions to the *Packaging and storage* section, according to PSD guidelines.

(PA5: A. Wilk) RTS—39699-1

Add the following:

■Doxazosin Mesylate



$C_{23}H_{25}N_5O_5 \cdot CH_4SO_3$ ~~547.59~~ 547.58

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(2,3-dihydro-1,4-benzodioxin-2-yl)carbonyl]-, monomethanesulfonate.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(1,4-benzodioxan-2-ylcarbonyl)piperazine monomethanesulfonate [*77883-43-3*].

» Doxazosin Mesylate contains not less than 98.0 percent and not more than 102.0 percent of $C_{23}H_{25}N_5O_5 \cdot CH_4SO_3$, calculated on the ~~anhydrous~~ dried basis.

Packaging and storage—Preserve in well-closed containers and store below 30°.

USP Reference standards ⟨11⟩—*USP Doxazosin Mesylate RS. USP Terazosin Related Compound A RS. USP Terazosin Related Compound C RS.*

Identification—

A: *Infrared Absorption* ⟨~~197M~~⟩⟨197K⟩.

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

Loss on drying ⟨731⟩—Dry at 105° under vacuum for 4 hours: it loses not more than 1.0% of its weight.

~~**Water,** *Method I* ⟨921⟩: not more than 1.0%.~~

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 20 µg per g.

Chromatographic purity~~—[To come.]~~

Solution A—Dissolve 17.3 g of sodium 1-octanesulfonate and 5.4 mL of phosphoric acid in 4 liters of water. Adjust with 1 M sodium hydroxide to a pH of 2.5, and mix.

Solution B—Use acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Dissolve 2.7 mL of phosphoric acid in 2 liters of water. Adjust with 1 M sodium hydroxide to a pH of 2.5, and mix.

Blank solution—Prepare a solution of dimethyl sulfoxide and *Diluent* (1 in 100).

System suitability solution—Prepare a solution containing about 1.5 µg of USP Terazosin Related Compound A RS per mL, 0.5 µg of USP Terazosin Related Compound C RS per mL, and 0.5 µg of USP Doxazosin Mesylate RS per mL in *Blank solution.*

Standard stock solution—To an accurately weighed quantity of USP Doxazosin Mesylate RS, add a volume of dimethyl sulfoxide, equivalent to about 1% of the flask volume, sonicate for one minute, and dilute quantitatively,

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and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL. Sonicate, if necessary, until dissolved.

Standard solution—Quantitatively, and stepwise if necessary, dilute a volume of *Standard stock solution* with *Blank solution* to obtain a solution containing 0.5 µg of doxazosin mesylate per mL.

Test solution—Transfer about 50 mg of Doxazosin Mesylate, accurately weighed, to a 100-mL volumetric flask, add 1 mL of dimethyl sulfoxide, and sonicate for 1 minute. Dilute with *Diluent* to volume and sonicate, if necessary, until dissolved.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatographic system is equipped with a 245-nm detector and a 4.0- × 80-mm column that contains packing L7. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (min.)	*Solution A* (%)	*Solution B* (%)	Elution
0–20	75→45	25→55	linear gradient
20–35	45	55	isocratic
35–36	45→75	55→25	linear gradient
36–47	75	25	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution between terazosin related compound C and doxazosin is not less than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections for the main peak is not more than ~~5.0%.~~ 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the percentage of each impurity in the portion of Doxazosin Mesylate taken by the formula:

~~$0.1F(C_S/C_T)(r_i/r_S)$,~~

$$100F(C_S/C_T)(r_i/r_S),$$

in which the response factor, *F,* is 0.6 for terazosin related compound A and 0.55 for terazosin related compound C; C_S is the concentration, in µg per mL, of USP Doxazosin Mesylate RS in the *Standard solution;* C_T is the concentration, in µg per mL, of doxazosin mesylate in the *Test solution;* r_i is the peak response for each individual impurity, excluding solvent peaks, obtained from the *Test solution;* and r_S is the peak response obtained from the *Standard solution:* not more than 0.3% of terazosin related compound A is found; not more than ~~0.1%~~ 0.25% of any other individual impurity is found; and not more than 1.0% of total impurities is found.

Assay—

~~*Buffer solution*—Prepare a 0.05 M solution of monobasic potassium phosphate by disolving 0.68 g of monobasic potassium phosphate in 100 mL of water. Adjust with phosphoric acid to a pH of 3.0 ± 0.1.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of *Buffer solution*, methanol, and acetonitrile (6:4:1.5). Make adjustments if necessary (see *System suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Doxazosin Mesylate RS in methanol to obtain a solution having a known concentration of about 0.30 mg per mL. Quantitatively dilute a volume of this solution~~

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~~with *Mobile phase* to obtain a solution having a known concentration of about 15.0 µg of USP Doxazosin Mesylate RS per mL.~~

~~*Assay preparation*—Transfer about 75 mg of Doxazosin Mesylate, accurately weighed, to a 250-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Quantitatively dilute a known volume of this solution with *Mobile phase* to obtain a solution having a concentration of about 15.0 µg per mL.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 246-nm detector and a 3.9-mm × 15.0-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k′, is not less than 4.5; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 10 µL) of the Standard preparation and the Assay preparation into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{23}H_{25}N_5O_5 \cdot CH_4SO_3$ in the portion of Doxazosin Mesylate taken by the formula:~~

~~$$5C(r_U/r_S),$$~~

~~in which C is the concentration, in µg per mL, of USP Doxazosin Mesylate RS in the Standard preparation; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

Buffer solution—Transfer 3.4 g of monobasic potassium phosphate into a 1-liter flask, and add 800 mL of water and 4.0 mL of triethylamine to dissolve. Adjust with phosphoric acid to a pH of 4.5, and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Buffer solution* (11:9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent:—~~Dissolve 2.7 mL of phosphoric acid in 2 liters of water. Adjust with 1 M sodium hydroxide to a pH of 2.5, and mix.~~ a mixture of methanol and 0.1 N hydrochloric acid (9:1).

Standard preparation—Dissolve an accurately weighed quantity of USP Doxazosin Mesylate RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a final concentration of about 49 µg per mL.

Assay preparation—Transfer about 98 mg of Doxazosin Mesylate to a 200-mL volumetric flask, dissolve in and dilute with *Diluent* to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 245-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute, and the column temperature is maintained at 40°. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′,* for doxazosin is not less than 2.0; the column efficiency is not less than 1000 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

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measure the responses for the doxazosin peaks. Calculate the quantity, in mg, of $C_{23}H_{25}N_5O_5 \cdot CH_4SO_3$ in the portion of Doxazosin Mesylate taken by the formula:

$$2C(r_U / r_S),$$

in which C is the concentration, in µg per mL, of USP Doxazosin Mesylate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Droperidol, *USP 26* page 674. Because of acquisition difficulty, it is proposed to remove USP 4,4′-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone RS from the *USP Reference standards* section and to revise the limit test accordingly to include the absorptivity value of the solution under test.

(PA3: S. Salado) RTS—40121-1

Change to read:

USP Reference standards ⟨11⟩—*USP Droperidol RS.* ~~*USP 4,4′-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]-butyrophenone RS.*~~

■■2S (*USP27*)

Change to read:

Limit of 4,4′-bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone—Dissolve about 30.0 mg of the sample in 70 mL of isopropyl alcohol in a 100-mL volumetric flask. Add 10.0 mL of 0.1 N hydrochloric acid, dilute with isopropyl alcohol to volume, and mix. ~~Concomitantly determine the absorbances of this solution and a Standard solution of USP 4,4′-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]-butyrophenone RS in the same medium at a concentration of 4.5 µg per mL,~~

■The absorptivity of the solution■2S (*USP27*) in 1-cm cells at the wavelength of maximum absorbance at about 330 nm, with a suitable spectrophotometer, using a 1 in 10 solution of 0.1 N hydrochloric acid in isopropyl alcohol as the blank ~~the absorbance of the test solution does not exceed that of the Standard solution, corresponding to not more than 1.5%.~~

■is not more than 0.7 (equivalent to limit of 1.5%).■2S (*USP27*)

BRIEFING

Dyphylline, *USP 26* page 677—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-11

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dyphylline RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Edetate Calcium Disodium, *USP 26* page 683—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-10

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Edetate Calcium Disodium RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Edetate Disodium, *USP 26* page 684—See Briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-11

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Edetate Disodium RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Edrophonium Chloride, *USP 26* page 685—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-12

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Edrophonium Chloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Enalapril Maleate, *USP 26* page 700. On the basis of comments received, it is proposed to make minor revisions to the test for *Related compounds*. It is also proposed to add storage conditions to the *Packaging and storage* section. In addition, a minor editorial style change has been made in the test for *Related compounds.*

(PA5: A. Wilk; PSD: C. Okeke) RTS—40005-1

Change to read:

Packaging and storage—Preserve in well-closed containers,

■and store at controlled room temperature.■2S (*USP27*)

Change to read:

Related compounds—

pH 6.8 phosphate buffer, pH 2.5 phosphate buffer, Solution A, Solution B, Mobile phase, Diluent, Enalapril diketopiperazine solution, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Enalapril Maleate RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 3 µg per mL.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak

■area■2S (*USP27*)
responses. Calculate the percentage of each impurity in the portion of Enalapril Maleate taken by the formula:

$$100(C_S / C_T)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Enalapril Maleate RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Enalapril Maleate in the *Test solution;* r_i is the peak ~~response~~

■area■2S (*USP27*)
of each impurity obtained from the *Test solution;* and r_S is the peak ~~response~~

■area■2S (*USP27*)
of enalapril obtained from the *Standard solution:* not more than 1.0% of ~~one individual impurity~~

■any impurity having a relative retention time of about 1.10■2S (*USP27*)
is found; not more than 0.3% of any other individual impurity is found; and not more than 2% of total impurities is found.

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BRIEFING

Ephedrine Sulfate, *USP 26* page 706—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-12

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Ephedrine Sulfate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Epinephrine, *USP 26* page 709—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-13

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Epinephrine Bitartrate RS. USP Norepinephrine Bitartrate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Ergoloid Mesylates Tablets, *USP 26* page 720 and page 626 of *PF* 29(3) [May–June 2003]. It is proposed to increase the volume of injection in the *Chromatographic system* used to quantify the dissolution samples to achieve an adequate sensitivity. Other changes are made to reflect the experimental conditions used. The column used in the experimental work is an XTerra RP 18 brand column of L1 packing.)

(PA3: S. Salado) RTS—39994-1

Change to read:

Dissolution ⟨711⟩ *(for Tablets intended to be swallowed)*—
Medium: water; 500 mL.
Apparatus 2: 50 rpm, the distance between the paddle blade and the inside bottom of the vessel being maintained at 4.5 ± 0.2 cm during the test.
Time: 30 minutes.

■Determine the amount of Ergoloid Mesylates dissolved using the following procedure.■2S (*USP27*)
Mobile phase—Prepare as directed in the *Assay.*
Standard solution—Dissolve an accurately weighed quantity of USP Ergoloid Mesylates RS in water to obtain a solution having a known concentration of about 50 µg per mL. Transfer 4 mL of this solution for every 0.5 mg of ergoloid mesylates contained in the Tablets to a 200-mL volumetric flask, add 1 mL of 0.1 N hydrochloric acid and 100 mL of water, mix, and dilute with water to volume.
Test solution—Transfer a 20-mL portion of the solution under test to a suitable container, add 100 µL of 0.1 N hydrochloric acid, and mix.
Chromatographic system—Proceed as directed in the *Assay* except that the sum of the relative standard deviation values for the four ergoloid mesylates peaks for replicate injections is not more than 3.0%.
Procedure—Separately inject equal volumes (about ~~200 µL~~ ■500 µL)■2S (*USP27*) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity of ergoloid mesylates as directed in the *Assay.*
Tolerances—Not less than 75% *(Q)* of the labeled amount of ergoloid mesylates is dissolved in 30 minutes.

Change to read:

Assay—
Mobile phase—Prepare a filtered and degassed solution containing a mixture of water, acetonitrile, and triethylamine (700:300:9). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).
Internal standard solution—Transfer about 113 mg of papaverine hydrochloride to a 1-liter flask. Add a mixture of 0.01 M tartaric acid and acetonitrile (2:1) to volume, and mix.
Standard preparation—Transfer about 33 mg of USP Ergoloid Mesylates RS, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with *Internal standard solution* to volume, and mix. Use a freshly prepared solution.
Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 5 mg of Ergoloid Mesylates to a 50-mL centrifuge tube. Add 15.0 mL of *Internal standard solution,* insert the stopper into the tube, and shake for about 15 minutes. Centrifuge, filter if necessary, and use the clear supernatant solution.
Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a ~~3.9-mm~~ ■4.6-mm■2S (*USP27*) × 15-cm column that contains packing L1.

■[NOTE—Use an L1 column capable of handling pH values greater than 11.]■2S (*USP27*)
The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency determined for the dihydro-β-ergocryptine mesylate peak is not less than 1000 theoretical plates; the tailing factor for dihydro-β-ergocryptine mesylate is not more than 2.0; the resolution, *R,* between the dihydro-α-ergocryptine mesylate and dihydroergocristine mesylate is not less than 2.0, the resolution, *R,* between dihydroergocristine and dihydro-β-ergocryptine is not less than 2.0; and the relative standard deviation of the ratio of the sum of the four peaks to the internal standard for replicate injections is not more than 1.5%.
Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The order of elution is papaverine, dihydroergocornine, dihydro-α-ergocryptine, dihydroergocristine, and dihydro-β-ergocryptine. Calculate the quantity, in mg, of ergoloid mesylates in the portion of Tablets taken by the formula:

$$15C(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Ergoloid Mesylates RS in the *Standard preparation;* and R_U and R_S are the sums of the ratios of responses of the four major peaks to the response of the internal standard peak obtained from the *Assay preparation* and the *Standard preparation,* respectively. Calculate the percentage of each of the individual alkaloids taken by the formula:

$$100R_i(MW)\text{yi}/\Sigma[R_i(MW)_i],$$

where R_i is the peak response ratio of the individual alkaloid to the internal standard; $(MW)_i$ is the molecular weight of the individual alkaloid; and $\Sigma[R_i(MW)_i]$ is the summation of the products of peak response ratios and molecular weights for the four alkaloids.

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BRIEFING

Ergonovine Maleate, *USP 26* page 721—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-7

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Ergonovine Maleate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Estradiol, *USP 26* page 742—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-8

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Estradiol RS. USP Estrone RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Conjugated Estrogens, *USP 26* page 747—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-9

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Estrone, *USP 26* page 750—See briefing under *Alprostadil.*

(PA1: C. Anthony) RTS—40156-10

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Estrone RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Ethacrynic Acid, *USP 26* page 754—See briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-13

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Ethacrynic Acid RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Fenoldopam Mesylate, *USP 26* page 776 and page 2964 of the *First Supplement*. On the basis of comments received, it is proposed to change the name of the test for *Organic volatile impurities* to *Limit of residual solvents.* See also briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-14

Change to read:

Packaging and storage—Preserve in tight containers, protected from moisture.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Fenoldopam Mesylate RS. USP Fenoldopam Related Compound A RS.

Change to read:

~~**Organic volatile impurities**~~

■**Limit of residual solvents**—■2S (*USP27*)

Internal standard solution—Prepare a solution, in organic-free water, containing 10 mg of *n*-butanol per mL. Transfer 100 µL of this solution to a 10-mL volumetric flask, dilute with dimethylsulfoxide to volume, and mix.

Standard solution—Prepare a solution, in organic-free water, containing 10 mg each of *n*-propanol, isopropyl alcohol, and dimethylformamide per mL. Transfer 100 µL of this solution to a 10-mL volumetric flask, dilute with *Internal standard solution* to volume, and mix.

Test solution—Transfer about 50 mg of Fenoldopam Mesylate, accurately weighed, to a 1-mL volumetric flask. Dilute with *Internal standard solution* to volume, and sonicate to dissolve completely.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.32-mm × 30-m fused-silica capillary column ■coated with a 1.8-µm film of stationary phase G43, and a split injection system. The carrier gas is helium, flowing at a rate of about 1 mL per minute through the column and a split ratio of about 50:1.■1S (*USP26*) The injection port and the detector temperatures are maintained at 140° and 260°, respectively. The column temperature is programmed as follows. It is maintained for 12 minutes at 40°, then increased at a rate of 8° per minute to 120°, held for 0.1 minute, then increased at a rate of 25° per minute to 180°, and maintained at that temperature for 8 minutes.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution,* dimethylsulfoxide, and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Identify, based on retention time, any peaks present in the chromatogram of the *Test solution.* Calculate the response factor, *F,* for each solvent in the *Standard solution* by the formula:

$$(W_R / W_I)(r_I / r_R),$$

in which W_R is the weight, in mg, of the solvent of interest; W_I is the weight, in mg, of the internal standard taken to prepare the *Internal standard solution;* and r_I and r_R are the peak responses for the internal standard and the solvent of interest, respectively, obtained from the *Standard solution.* Calculate the percentage, by weight, of each solvent found in the *Test solution* by the formula:

$$100FD(r_i / r_S)(W_I / W_D),$$

in which F is the average response factor for the solvent of interest obtained from all injections of the *Standard solution; D* is the dilution factor for the internal standard in the *Test solution* (i.e., 0.0001); r_i and r_S are the peak responses for the solvent of interest and the internal standard, respectively, obtained from the *Test solution; W_I* is the weight, in mg, of the internal standard taken to prepare the *Internal standard solution;* and W_D is the weight, in mg, of Fenoldopam Mesylate taken to prepare the *Test solution:* not more than 0.2% of total ~~organic volatile impurities~~

■residual solvents■2S (*USP27*)
is found.

Add the following:

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

BRIEFING

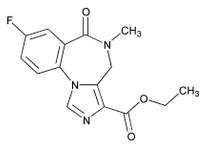
Flumazenil; Flumazenil Injection. Because there are no existing *USP* monographs for this drug substance and dosage form, new monographs, based on validation data received, are being proposed. The liquid chromtographic procedures in the *Assay* and in the *Related compounds Test 2* were validated using a Zorbax RX C-8 brand of L7 column. Typical retention times reported are about 7 minutes for flumazenil, about 2 minutes for flumazenil related compound A, and about 6 minutes for flumazenil related compound B.

(PA3: S. Salado) RTS—39640-1

In-Process Revision

Add the following:

■Flumazenil



$C_{15}H_{14}FN_3O_3$ 303.3

4*H*-Imidazo[1,5-α][1,4]benzodiazepine-3-carboxylic acid, 8-fluoro-5,6-dihydro-5-methyl-6-oxo-, ethyl ester.

Ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazo[1,5-α][1,4]benzodiazepine-3-carboxylate [*78755-81-4*].

» Flumazenil contains not less than 98.0 percent and not more than 102.0 percent of $C_{15}H_{14}FN_3O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Flumazenil RS. USP Flumazenil Related Compound A RS. USP Flumazenil Related Compound B RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Diluent, Adsorbent, Test solution, Standard solution 1, Application volume, and Developing solvent system—Proceed as directed for *Related compounds Test 1*.

Melting range, *Class Ia* ⟨741⟩: between 198° and 202°.

Bacterial endotoxins ⟨85⟩—It contains not more than 25.0 USP Endotoxin Units per mg of Flumazenil.

Water, *Method I* ⟨921⟩: not more than 0.5%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Related compounds—

TEST 1—

Ninhydrin solution—Dissolve 0.5 g of ninhydrin in 90 mL of alcohol, and add 10 mL of glacial acetic acid.

Diluent—Prepare a mixture of alcohol and chloroform (1:1).

Adsorbent—0.25-mm layer of chromatographic silica gel mixture (see *Chromatography* ⟨621⟩).

Test solution—Transfer about 250 mg of Flumazenil, accurately weighed, to a 5-mL volumetric flask. Dissolve in and dilute with *Diluent* to volume, and mix.

Standard solution 1—Dissolve an accurately weighed portion of USP Flumazenil RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 50 mg per mL.

Standard solution 2—Prepare a solution of USP Flumazenil RS, USP Flumazenil Related Compound A RS, USP Flumazenil Related Compound B RS, and *N,N*-dimethylformamide diethyl acetal in *Diluent* having known concentrations of about 0.5 mg per mL, about 0.5 mg per mL, about 0.5 mg per mL, and about 0.6 µL per mL respectively.

Standard solution 3—Dilute 2.0 mL of *Standard solution 2* with *Diluent* to 10.0 mL.

Standard solution 4—Dilute 1.0 mL of *Standard solution 2* with *Diluent* to 10.0 mL.

Standard solution 5—Dilute 0.5 mL of *Standard solution 2* with *Diluent* to 10.0 mL.

Application volume: 10 µL.

Developing solvent system: a mixture of chloroform, glacial acetic acid, alcohol, and water (75:15:7.5:2.5).

In-Process Revision

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Dry the plate for 10 minutes in a current of cold air, and view under short wavelength UV light. Spray the plate with *Ninhydrin solution,* and heat at 105° for 15 minutes. The R_F values of analytes are as follows:

Compound	R_F	Detection
Flumazenil	about 0.8	UV
Flumazenil related compound B	about 0.7	UV
Flumazenil related compound A	about 0.1	UV
N,N-Dimethylformamide diethyl acetal	about 0.04	Ninhydrin

Any spot at an R_F value corresponding to *N,N*-dimethylformamide diethyl acetal in the chromatogram obtained from the *Test solution* is not more intense than the corresponding spot in the chromatogram obtained from *Standard solution 3:* not more than 0.2% is found. Compare any unspecified spot in the chromatogram of the *Test solution* with the spot for flumazenil obtained in the chromatograms of *Standard solution 3, Standard solution 4,* and *Standard solution 5,* when viewed under UV light. Report the approximate level of each of the unknown impurities: not more than 0.2% of any unknown impurity is found; and not more than 0.5% of total unknown impurities is found. [NOTE—Use the spots for flumazenil related compound A and flumazenil related compound B in the chromatograms of *Standard solution 3, Standard solution 4,* and *Standard solution 5* as references only. They are quantified in *Test 2*.]

TEST 2—

Diluted phosphoric acid pH 2.0, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Use the *Standard preparation* described in the *Assay.*

Test solution—Use the *Assay preparation* described in the *Assay.*

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Flumazenil taken by the formula:

$$(10{,}000F)(C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Flumazenil RS in the *Standard solution; F* is the relative response factor of the impurity according to the table below; W is the weight, in mg, of Flumazenil, on the anhydrous basis, used to prepare the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for flumazenil in the *Standard solution:* the impurities meet the requirements given in the table below.

Compound name	Relative retention time	Relative Response Factor	Limit (%)
Flumazenil related compound A	about 0.23	0.9	0.2
Flumazenil related compound B	about 0.45	0.9	0.3
Flumazenil	1.0	—	—
Unknown impurities	—	1.0	0.2
Total	—	—	0.5

In-Process Revision

Limit of alcohol and methylene chloride—

Standard solution— Prepare a solution in dimethylsulfoxide containing 100 µg per mL of dehydrated alcohol and 1 µg per mL of methylene chloride. Transfer 1 mL of this solution to a 20-mL gas chromatographic headspace vial, and cap immediately.

Test solution—Transfer about 100 mg of Flumazenil, accurately weighed, to a 20-mL gas chromatographic headspace vial, add 1.0 mL of dimethyl sulfoxide, cap immediately, and swirl.

Chromatographic system (see *Chromatography* ⟨621⟩)— The gas chromatograph is equipped with a headspace injector and a flame-ionization detector, a 0.32-mm × 30-m fused-silica capillary column bonded with a 1.8-µm layer of phase G43, and a split injection system. The carrier gas is helium, flowing at a rate of about 1.7 mL per minute, and the total flow rate is about 40 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at about 40° for 20 minutes, then the temperature is increased at a rate of 35° per minute to 240°, and maintained at 240° for 20 minutes. The injection port temperature is maintained at about 140°, and the detector is maintained at about 260°. The *Standard solution* and the *Test solution* are maintained at about 90°, and the needle and transfer temperatures are maintained at about 140°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the elution order is alcohol and methylene chloride; the resolution, *R,* between alcohol and methylene chloride is not less than 3.0; and the relative standard deviation of consecutive injections is not more that 10.0%.

Procedure—Using a heated, gas-tight syringe, separately inject equal volumes (about 1 mL) of the headspace of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of alcohol and methylene chloride in the portion of Flumazenil taken by the formula:

$$100(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of the relevant analyte in the *Standard solution; W* is the weight, in mg, of Flumazenil taken to prepare the *Test solution;* and r_U and r_S are the peak areas of the corresponding analyte obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of alcohol and not more than 0.001% of methylene chloride is found.

Assay—

Diluted phosphoric acid, pH 2.0—Adjust 800 mL of water with phosphoric acid to pH 2.0 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Diluted phosphoric acid, pH 2.0* and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Flumazenil RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

System suitability solution—Dissolve appropriate quantities of USP Flumazenil Related Compound A RS and USP Flumazenil Related Compound B RS in the *Standard preparation,* and dilute quantitatively, and stepwise if necessary, with *Standard preparation* to obtain a solution having known concentrations of each of about 0.2 µg per mL.

Assay preparation—Transfer about 10.0 mg of Flumazenil, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 15-cm column that contains packing

L7. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.23 for flumazenil related compound A, about 0.45 for flumazenil related compound B, and 1.0 for flumazenil; the resolution, *R,* between flumazenil related compound B and flumazenil is not less than 3.0; and the tailing factor is not more than 1.5 for the flumazenil peak. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area for the flumazenil peaks. Calculate the quantity, in mg, of $C_{15}H_{14}FN_3O_3$ in the portion of Flumazenil taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Flumazenil RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Flumazenil Injection—See briefing under *Flumazenil*. The *Assay* and *Related compounds* test were validated using a YMC–Pack CN brand of L10 column. The retention times are about 7 minutes for flumazenil, about 5 minutes for flumazenil related compound A, and about 6 minutes for flumazenil related compound B.

(PA3: S. Salado) RTS—39640-2

In-Process Revision

Add the following:

■Flumazenil Injection

» Flumazenil Injection is a sterile solution of Flumazenil. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of flumazenil ($C_{15}H_{14}FN_3O_3$).

Packaging and storage—Preserve in tight, single-dose containers, preferably of Type I glass, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Flumazenil RS. USP Flumazenil Related Compound A RS. USP Flumazenil Related Compound B RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩

Adsorbent—0.25-mm layer of chromatographic silica gel mixture containing a fluorescent indicator.

Test solution—Dilute, if necessary, a volume of injection with water to obtain a solution containing 0.1 mg of Flumazenil per mL.

Standard solution—Prepare a solution in methanol, and dilute, step wise if necessary, with water to obtain a solution containing about 0.1 mg of USP Flumazenil RS per mL in a mixture of water and methanol (9:1).

Developing solvent system: a mixture of ethyl acetate and methanol (9:1).

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

Bacterial endotoxins ⟨85⟩: not more than 25.0 USP Endotoxin Units per mg of flumazenil.

pH ⟨791⟩: between 3.4 and 4.6.

Particulate matter ⟨788⟩: meets the requirements for small-volume injections.

Related compounds—

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

Standard solution—Use the *Standard preparation* as described in *Assay.*

Test solution—Use the *Assay preparation* as described in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of each impurity in the portion of Injection taken by the formula:

$$100(V/D)(F)(C/L)(r_i / r_S),$$

in which V is the volume, in mL, of the *Test Solution; C* is the concentration, in mg per mL, of USP Flumazenil RS in the *Standard solution; L* is the dose, in mg, of Flumazenil per mL obtained in the *Assay; D* is the volume, in mL, of Injection taken to prepare the *Test solution; F* is the relative response factor as described in the table below; r_i is the peak response for each impurity in the *Test solution;* and r_S is the peak response of flumazenil obtained from the *Standard solution:* meets the requirements given in the table below.

Compound name	Relative Response Factor	Limit (%)
Flumazenil related compound A	0.9	1.0
Unknown	1.0	0.5
Total unknown	—	1.0
Total	—	2.0

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Diluent—Prepare a mixture of water, tetrahydrofuran, and methanol (75:20:5).

0.02 M Phosphate buffer—Add 0.02 M phosphoric acid to 0.02 M monobasic potassium phosphate to obtain a solution having a pH of 2.7 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *0.02 M Phosphate buffer,* tetrahydrofuran, and methanol (75:20:5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve appropriate quantities of USP Flumazenil RS, USP Flumazenil Related Compound A RS, and USP Flumazenil Related Compound B RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having known concentrations of about 0.01 mg of each per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Flumazenil RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Dilute a volume of Injection, if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.1 mg per mL of flumazenil in a known volume, *V.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 230-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L10. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak areas as directed for *Procedure:* the relative retention times are about 0.71 for flumazenil related compound A, about 0.85 for flumazenil related compound B, and 1.0

In-Process Revision

for flumazenil; the resolution, *R,* between flumazenil related compound B and flumazenil is not less than 1.8; and the tailing factor for flumazenil related compound A is not more than 2.0. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of flumazenil ($C_{15}H_{14}FN_3O_3$) in the volume of Injection taken by the formula:

$$VC(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Flumazenil RS in the *Standard preparation; V* is the volume, in mL, of the *Assay preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP27*)

BRIEFING

Fluoxetine Delayed-Release Capsules, page 403 of *PF* 29(2) [Mar.–Apr. 2003]. It is proposed to change the acid solution used to prepare the *Degraded fluoxetine solution* in the *Chromatographic purity* test to reflect the actual acid solution used in the method.

(PA3: S. Salado) RTS—40035-1

In-Process Revision

Add the following:

■Fluoxetine Delayed-Release Capsules

» Fluoxetine Delayed-Release Capsules contain an amount of Fluoxetine Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fluoxetine ($C_{17}H_{18}F_3NO$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Fluoxetine Hydrochloride RS. USP Fluoxetine Related Compound C RS.*

Identification, *Infrared Absorption* ⟨197F⟩—

Test specimen—Transfer the contents of 3 Capsules to a suitable container, and grind to a fine powder. Transfer ~~an accurately weighed~~ a portion of the powder, equivalent to about 40 mg of fluoxetine, to a suitable container, and dissolve in 25 mL of 0.1 N hydrochloric acid. Filter, and transfer 10 mL of the solution so obtained to a separatory funnel, add 20 mL of methylene chloride, and mix. Allow the phases to separate, and transfer the organic layer to a small glass container. Evaporate to dryness with the aid of a current of air and mild heat. Redissolve the residue with a few drops of methylene chloride, and transfer to a potassium bromide plate. Dry or evaporate to a thin film with the aid of a stream of nitrogen.

Drug release ⟨724⟩—[To come.]

Uniformity of dosage units ⟨905⟩: meet the requirements.

Chromatographic purity—

Ion-pair solution—Dissolve about 6.5 g of sodium 1-octanesulfonate and 2.9 g of anhydrous sodium acetate in 1 liter of water, and adjust with glacial acetic acid to a pH of 5.0.

Mobile phase—Prepare a filtered and degassed mixture of *Ion-pair solution* and acetonitrile (58:42). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Degraded fluoxetine solution—Dissolve ~~an accurately weighed~~ a quantity of USP Fluoxetine Hydrochloride RS in ~~0.1 N hydrochloric acid~~ 1.0 N sulfuric acid to obtain a solution containing about 2.2 mg per mL. Heat to 85° for 3 hours, and cool to room temperature.

Fluoxetine related compound solution—Dissolve ~~an accurately weighed~~ a quantity of USP Fluoxetine Related Compound C RS in *Mobile phase* to obtain a solution containing about 0.5 mg per mL.

System suitability solution—Transfer ~~an accurately weighed quantity of~~ about 13.5 mg of USP Fluoxetine Hydrochloride RS to a 100-mL volumetric flask, add 2 mL of *Degraded fluoxetine solution* and 2 mL of *Fluoxetine related compound solution,* and dissolve in and dilute with *Mobile phase* to volume. Transfer 10.0 mL of this solution to a 250-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Detector sensitivity solution—Transfer 1 mL of the *System suitability solution* to a 100-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solution—Weigh and finely powder not fewer than 20 Capsules. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of fluoxetine, to a 250-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Filter before injection.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.6-mm × 15-cm column that contains 3.5-µm packing L7. The column temperature is maintained at 30°. The flow rate is about 1 mL per minute. Inject the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.49 for α,α,α-trifluoro-*p*-cresol, 0.70 for fluoxetine related compound C, and 1.0 for fluoxetine; the resolution, *R,* between α,α,α-trifluoro-*p*-cresol and fluoxetine related compound C is not less than 2.0, and the resolution, *R,* between fluoxetine related compound C and fluoxetine is not less than 6.0. Chromatograph the *Detector sensitivity solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the fluoxetine peak is not less than 10.

Procedure—Inject a volume (about 50 µL) of the *Test solution* into the chromatograph, record the chromatogram for at least three times the retention time of the fluoxetine peak, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all the peaks: not more than 0.2% of any individual impurity is found, and not more than 0.7% of total impurities is found.

Assay—

Ion-pair solution—Dissolve about 2.9 mL of glacial acetic acid and about 7.1 g of sodium 1-pentanesulfonate in 1 liter of water. Adjust with 5 N sodium hydroxide to a pH of 5.0.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Ion-pair solution* (67:33). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve ~~accurately weighed~~ suitable quantities of USP Fluoxetine Hydrochloride RS and α,α,α-trifluoro-*p*-cresol in *Mobile phase* to obtain a solution containing about 110 µg per mL and 20 µg per mL, respectively.

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Standard preparation—Dissolve an accurately weighed quantity of USP Fluoxetine Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.11 mg per mL.

Assay preparation—Remove, as completely as possible, the contents of not fewer than 20 Capsules, and mix. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of fluoxetine, to a 500-mL volumetric flask, shake by mechanical means for about 10 minutes, and then sonicate for about 5 minutes. Cool the solution to room temperature, dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 10.0-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix. Filter the solution before injection.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 7.5-cm column that contains 3.5-µm packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 38°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for α,α,α-trifluoro-*p*-cresol and 1.0 for fluoxetine; the resolution, *R,* between α,α,α-trifluoro-*p*-cresol and fluoxetine is not less than 4.0; the tailing factor for the fluoxetine peak is not more than 1.7; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of fluoxetine ($C_{17}H_{18}F_3NO$) in the portion of Capsules taken by the formula:

$$1000(309.33/345.79)C(r_U/r_S),$$

in which 309.33 and 345.79 are the molecular weights of fluoxetine and fluoxetine hydrochloride, respectively; C is the concentration, in mg per mL, of USP Fluoxetine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Flutamide, *USP 26* page 830 and page 405 of *PF* 29(2) [Mar.–Apr. 2003]; **Flutamide Capsules,** *USP 26* page 830 and page 407 of *PF* 29(2) [Mar.–Apr. 2003]. In the *Procedure* sections of the test for *Related compounds* and in the *Assay* it is proposed to add the words "area" and "response", as appropriate, to specify peak area responses. It is also proposed to make several other changes for further clarification of these test methods. In addition, minor editorial style changes have been made.

(PA1: C. Anthony) RTS—40123-1

Change to read:

Loss on drying ⟨731⟩—Dry it in vacuum at 60° for 3 hours; it loses not more than ~~1.0%~~

■0.5%■2S (*USP27*)
of its weight.

Delete the following:

■~~**Chromatographic purity**~~

~~*Mobile phase*—Proceed as directed in the *Assay.*~~

~~*System suitability solution*—Dissolve suitable quantities of USP *o*-Flutamide RS and USP Flutamide RS in *Mobile phase* to obtain a solution containing about 0.004 and 2 mg per mL, respectively.~~

~~*Test solution*—Dissolve an accurately weighed quantity of Flutamide in acetonitrile to obtain a solution containing about 2 mg per mL.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 0.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed under *Procedure:* the relative retention times are about 1.4 for *o*-flutamide and 1.0 for flutamide, the resolution, *R,* between flutamide and *o*-flutamide is not less than 2.0, and the relative standard deviation for replicate injections is not more than 6.0% for *o*-flutamide.~~

~~*Procedure*—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, and run the chromatograph until the *o*-flutamide peak has eluted. Record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Flutamide taken by the formula:~~

~~$100(r_i/r_S)$,~~

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~~in which r_i is the peak response for each impurity, and r_s is the sum of the responses of all of the peaks: not more than 0.5% of total impurities is found.~~ ■2S (*USP27*)

Add the following:

■**Related compounds**—

Mobile phase and *System suitability solution*—Prepare as directed in the *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

~~*Sensitivity solution*~~ —*Detector sensitivity solution*—Transfer 1.0 mL of the *Standard solution* into a 100-mL volumetric flask, dilute with a mixture of water and acetonitrile (4:1) to volume, and mix. Dilute quantitatively, and stepwise if necessary, with a mixture of water and acetonitrile (4:1) to obtain a solution having a known concentration of about 0.1 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 25 ± 5°. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak area responses as directed for *Procedure:* the relative retention times are about 1.4 for *o*-flutamide and 1.0 for flutamide; and the resolution, *R,* between flutamide and *o*-flutamide is not less then 6.0. Chromatograph the ~~*Sensitivity solution, Detector sensitivity solution,*~~ and record the peak area responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10.0% for ~~*o*-flutamide~~ flutamide.

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, ~~and run the chromatogram until the *o*-flutamide peak has eluted.~~ record the chromatogram, and measure the peak area responses. Calculate the percentage of each impurity in the portion of Flutamide taken by the formula:

~~$100(Fr_i/r_s)$,~~

$$100(1/F)(r_i/r_s),$$

in which F is the relative response factor of the impurities according to the table below; r_i is the peak area response for each impurity; and r_s is the sum of the responses of all the peaks: the impurities meet the requirements tabulated below.

Compound name	Relative retention time	Relative Response Factor (F)	Limit (%)
4-Nitro-3-trifluoromethylacetanilide	0.42	1.06	0.2
4-Nitro-3-trifluoromethylaniline	0.45	1.10	0.15
3-trifluoromethylaniline	0.63	1.10	0.2
4-Nitro-3-trifluoromethylpropionanilide	0.66	1.02	0.3
3-trifluoromethylisobutyranilide	0.80	1.95	0.2
o-Flutamide	1.40	1.78	0.2
Flutamide	1.0	1.0	—
Unknown	—	1.0	0.05
Total unknown			0.1
Total impurities	—	—	~~0.5~~ 0.4

■2S (*USP27*)

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile ~~(1:1).~~

■(55:45).■2S (*USP27*)

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Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Flutamide RS in ~~*Mobile phase*, and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.~~

■50 mL of acetonitrile, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.2 mg per mL.■2S (*USP27*)

System suitability solution—~~Dissolve suitable quantities of USP o-Flutamide RS and USP Flutamide RS in *Mobile phase* to obtain a solution containing about 0.4 and 0.5 mg per mL, respectively.~~

■Transfer about 50 mg of USP *o*-Flutamide RS accurately weighed to a 50-mL volumetric flask, dissolve in 10 mL of acetonitrile, dilute with water to volume, and mix. Transfer 1.0 mL of this solution and 5.0 mL of the *Standard preparation* into a 100-mL volumetric flask, dilute with a mixture of water and acetonitrile (4:1) to volume, and mix.■2S (*USP27*)

Assay preparation—~~Transfer about 50 mg of Flutamide, previously dried and accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.~~

■Transfer about 50 ~~µg~~ mg of Flutamide, previously dried and accurately weighed, to a 250-mL volumetric flask. Add 50 mL of acetonitrile, and sonicate until the Flutamide dissolves. Add 150 mL of water, mix, and allow to warm to room temperature. Dilute with water to volume, and mix.■2S (*USP27*)

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L1.

■The column temperature is maintained at 25 ± 5°.■2S (*USP27*)

The flow rate is about ~~0.5~~

■1.0■2S (*USP27*)
mL per minute. Chromatograph the *System suitability solution,* and record the peak

■area■2S (*USP27*)
responses as directed for *Procedure:* the relative retention times are about 1.4 for *o*-flutamide and 1.0 for flutamide; and the resolution, *R,* between flutamide and *o*-flutamide is not less than ~~2.0.~~

■6.0.■2S (*USP27*)
Chromatograph the *Standard preparation,* and record the peak

■area■2S (*USP27*)
responses as directed for *Procedure:*

■the tailing factor is not more than 2.0; and■2S (*USP27*)
the relative standard deviation for replicate injections is not more than ~~1.0%.~~

■1.5%.■2S (*USP27*)

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{11}H_{11}F_3N_2O_3$ in the portion of Flutamide taken by the formula:

~~$100C(r_U/r_S)$,~~

■$250C(r_U/r_S)$,■2S (*USP27*)

in which C is the concentration, in mg per mL, of USP Flutamide RS in the *Standard preparation;* and r_U and r_S are the peak

■area■2S (*USP27*)
responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Flutamide Capsules, *USP 26* page 830 and page 407 of *PF* 29(2) [Mar.–Apr. 2003]—See briefing under *Flutamide.*

(PA: 1 C. Anthony) RTS—40123-2

Change to read:

Uniformity of dosage units ⟨905⟩: meet the requirements.~~, the following procedure for content uniformity being used.~~

~~*Procedure for content uniformity*—Empty the contents of 1 Capsule into a 50-mL centrifuge tube, place the empty capsule shell into the tube, and mix. Add 40.0 mL of a mixture of methanol and water (95:5), agitate for 30 minutes, and clarify by centrifuging. Transfer 1.0 mL of the supernatant liquid to a 100-mL volumetric flask, and dilute with a mixture of methanol and water (95:5) to volume to obtain a solution containing about 0.03 mg of flutamide per mL. Concomitantly determine the absorbances of this solution and a solution of USP Flutamide RS in the same solvent having a known concentration of about 0.03 mg per mL, in 1-cm cells at the wavelength of maximum absorbance at 299 nm, using a mixture of methanol and water (95:5) as the blank. Calculate the quantity, in mg, of $C_{11}H_{11}F_3N_2O_3$ in the Capsule taken by the formula:~~

~~$(TC/D)(A_U/A_S)$,~~

~~in which T is the labeled quantity, in mg, of flutamide in the Capsule; C is the concentration, in mg per mL, of USP Flutamide RS in the Standard solution; D is the concentration, in mg per mL, of flutamide in the solution from the Capsule, based on the labeled quantity per Capsule and the extent of dilution; and A_U and A_S are the absorbances of the solution from the Capsule and the Standard solution, respectively.~~

■■2S (*USP27*)

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Add the following:

■**Chromatographic purity—**

Mobile phase—Prepare as directed in the *Assay.*

Standard solution—Prepare as directed in the *Assay* for *Standard preparation.*

Test solution—Use the *Assay preparation.*

~~*Sensitivity solution*~~ *Detector sensitivity solution*—Transfer an accurately measured volume of the *Standard solution* into a volumetric flask, and dilute quantitatively, and stepwise if necessary, with a mixture of water and acetonitrile (4:1) to obtain a solution having a known concentration of about 0.2 µg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The column temperature is maintained at 25 ± 5°. The flow rate is about ~~+~~ 1.0 mL per minute. Chromatograph the ~~*Sensitivity solution,*~~ *Detector sensitivity solution* and record the peak area responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10% for flutamide.

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak area responses. Calculate the percentage of each impurity in the portion of Capsules taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak area response for each impurity; excluding those where peak area responses are less than those obtained from the *Detector sensitivity solution;* and r_s is the sum of the responses of all the peaks: not more than 0.2% for any impurity having a relative retention time of about 0.45 is found; not more than 0.1% of any other impurity is found; and not more than 0.3% of total impurities is found.■2S (*USP27*)

Change to read:

Assay—

■*Diluent*—Prepare a mixture of acetronitrile and water (1:1).■2S (*USP27*)

Mobile phase—~~Prepare a filtered and degassed mixture of methanol and 0.05 *M* monobasic potassium phosphate (7:4).~~

■Prepare a filtered and degassed mixture of water and acetonitrile (55:45).■2S (*USP27*)

Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Flutamide RS in ~~methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.18 mg per mL.~~

■*Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 0.5 mg per mL. Transfer 20.0 mL of this solution into a 50-mL volumetric flask, and dilute with water to volume to obtain a final concentration of 0.2 mg per mL.■2S (*USP27*)

~~*System suitability solution*—Dissolve suitable quantities of testosterone and USP Flutamide RS in methanol to obtain a solution containing about 0.09 and 0.18 mg per mL, respectively.~~

■■2S (*USP27*)

Assay preparation—Remove the contents of not fewer than 20 Capsules, and ~~grind the contents to a fine powder. Transfer an accurately weighed portion of powder, equivalent to about 60 mg of flutamide, to a 50-mL screw-capped centrifuge tube. Add 20 mL of a mixture of methanol and water (95:5), agitate for 30 minutes, and clarify by centrifuging. Transfer 3.0 mL of the supernatant liquid to a 50-mL volumetric flask, dilute with methanol to volume, and mix.~~

■mix. Transfer an accurately weighed portion of the powder, equivalent to 125 mg of flutamide, into a 250-mL volumetric flask. Add 180 mL of *Diluent.* Shake the flask for 15 minutes. Dilute with *Diluent* to volume, and mix. Allow the insoluble material to settle. Transfer 20.0 mL of supernatant into a 50-mL volumetric flask, dilute with water to volume, mix, and pass through a polytef membrane filter having a 0.45-µm ~~or finer~~ porosity.■2S (*USP27*)

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~254-nm detector and a 3.9-mm × 30-cm~~

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■240-nm detector and a 4.6-mm × 25-cm■2S (*USP27*) column that contains packing L1.

■The column temperature is maintained at 25 ± 5°.■2S (*USP27*)

The flow rate is about 1.0 mL per minute. Chromatograph the ~~*System suitability solution,* and record the peak responses as directed under *Procedure:* the relative retention times are about 1.2 for testosterone and 1.0 for flutamide, and the resolution, *R,* between flutamide and testosterone is not less than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed under *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.~~

■*Standard preparation,* and record the peak area response as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.■2S (*USP27*)

Procedure—Separately inject equal volumes ~~(about 10 µL)~~

■(about 20 µL)■2S (*USP27*) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the ~~responses for the major peaks.~~

■peak area response for the flutamide peak.■2S (*USP27*) Calculate the quantity, in mg, of $C_{11}H_{11}F_3N_2O_3$ in the portion of Capsules taken by the formula:

~~$333.3C(r_U/r_S),$~~

■$625C(r_U/r_S),$■2S (*USP27*)

in which C is the concentration, in mg per mL, of USP Flutamide RS in the *Standard preparation;* and r_U and r_S are the peak

■area■2S (*USP27*) responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Fosphenytoin Sodium, *USP 26* page 833. It is proposed to modify the *Related compounds* test to indicate which reference standard should be used for calculating unknown impurities. **Fosphenytoin Sodium Injection,** page 68 of *PF* 29(1) [Jan.–Feb. 2003]. Because 2,2-diphenylglycine is now available as USP Phenytoin Related Compound A RS, it is proposed to make changes in the corresponding monographs to reflect this availability.

(PA3: S . Salado) RTS—40065-1; 39907-2

Change to read:

USP Reference standards ⟨11⟩—*USP Fosphenytoin Sodium RS. USP Phenytoin RS.*

■*USP Phenytoin Related Compound A RS.*■2S (*USP27*) *USP Phenytoin Related Compound B RS.*

Change to read:

~~**Chromatographic purity**~~

■**Related compounds**—■2S (*USP27*)

Buffer solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of ~~2,2-diphenylglycine,~~

■USP Phenytoin Related Compound A RS,■2S (*USP27*) USP Phenytoin Related Compound B RS, and USP Phenytoin RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 3.0 µg per mL, 3.0 µg per mL, and 1.5 µg per mL, respectively.

Test solution—Transfer about 150 mg of Fosphenytoin Sodium, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for not less than six times the retention time of the major peak, and measure all of the peak responses. Calculate the percentage of phenytoin, phenytoin related compound B, and ~~2,2-diphenylglycine,~~

■phenytoin related compound A,■2S (*USP27*) if present, in the portion of Fosphenytoin Sodium taken by the formula:

$$100(C_S/C_U)(r_i/r_S),$$

in which C_S is the concentration, in mg per mL, of ~~USP Phenytoin RS~~

■the USP Reference Standard of the respective impurity■2S (*USP27*) in the *Standard solution;* C_U is the concentration, in mg per mL, of Fosphenytoin Sodium in the *Test solution;* and r_i and r_S are the peak responses for each impurity obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of phenytoin is found; not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.

■[NOTE—Use the peak area and concentration of USP Phenytoin RS in the *Standard solution* as r_S and C_S, respectively, to calculate the percentage of the unknown impurities.]■2S (*USP27*)

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BRIEFING

Fosphenytoin Sodium Injection, page 68 of *PF* 29(1) [Jan.–Feb. 2003]—It is proposed to add a *Labeling* requirement that is intended to ensure that dosages of oral Phenytoin Sodium are correctly related to the amounts of Fosphenytoin Sodium administered previously by injection. Clarity of labeling the container, which is to avoid the need to perform molecular weight-based adjustements, is expected to alleviate problems with converting between fosphenytoin sodium and phenytoin sodium doses.

The revision is proposed for publication in the *Second Supplement to USP27–NF22,* which is to become official August 1, 2004, but with February 1, 2006, designated as the official date for the *Labeling* requirement. Use of the *Labeling* requirement would be permitted as of August 1, 2004, but the *Labeling* requirement would not become mandatory until February 1, 2006. The eighteen-month postponement of the official date for the *Labeling* requirement is intended to allow for product label changes to be made and for health-care professionals and patients to become familiar with the labeling provisions.

See also the briefing under *Fosphenytoin Sodium.*

(PA3: S. Salado; NL: C. Barnstein) RTS—39907-3; 40223-1

Add the following:

■Fosphenytoin Sodium Injection

» Fosphenytoin Sodium Injection is a sterile solution of Fosphenytoin Sodium in Water for Injection. Fosphenytoin Sodium is a prodrug. Injection containing 1 mg per mL of Fosphenytoin Sodium is equivalent to 0.667 mg per mL of Phenytoin Sodium after injection. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of fosphenytoin sodium ($C_{16}H_{13}N_2Na_2O_6P$).

Packaging and storage—Preserve in single-dose or multiple-dose containers, preferably of Type I glass. ~~protected from light.~~ Store between 2° and 8°. Do not store at room temperature for more than 48 hours.

Labeling—Both the actual content of Fosphenytoin Sodium and the content of Phenytoin Sodium, expressed in terms of phenytoin sodium equivalents, are stated prominently on the label.

(Official February 1, 2006)

USP Reference standards ⟨11⟩—*USP Fosphenytoin Sodium RS. USP Phenytoin RS. USP Phenytoin Related Compound A RS. USP Phenytoin Related Compound B RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—

Test specimen—Transfer a 5-mL aliquot of Injection to a 100-mL beaker, add 30 mL of acetone to form a white precipitate, and stir for 20 minutes using a magnetic stirrer. Filter in vacuum, and collect the precipitate using suitable filter paper. Allow to dry in vacuum for 15 minutes.

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

Bacterial endotoxins ⟨85⟩: not more than 14 USP Endotoxin Units per mL.

pH ⟨791⟩: between 8.3 and 9.3.

~~**Chromatographic purity—**~~

~~*Buffer solution, Mobile phase, System suitability solution,* and *Chromatographic system*—Proceed as directed in the *Assay.*~~

~~*Standard solution*—Dissolve an accurately weighed quantity quantities of USP Fosphenytoin RS, 2,2-diphenylglycine, USP Phenytoin Related Compound B RS, and USP Phenytoin RS in *Buffer solution* methanol, and dilute quantitatively, and stepwise if necessary, with *Buffer solution* to obtain a solution having a known concentrations of about 150.0, 0.3, 2.25, 750.0, 1.5, 11.25, and 0.3–1.5 µg per mL, respectively.~~

~~*Test solution*—Use the *Assay preparation.*~~

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~~*Procedure*—Separately inject equal volumes (about 20 µL–40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for not less than six times the retention time of the major peak, and measure all of the peak responses. Calculate the percentage of each impurity in the volume of Injection taken by the formula:~~

~~$$100(C_S/C_U)(r_i/r_S),$$~~

~~phenytoin, phenytoin related compound B, and 2,2-diphenylglycine in the volume of Injection taken by the formula:~~

~~$$100(r_i/r_S),$$~~

~~in which C_S is the concentration, in mg per mL, of USP Phenytoin RS in the *Standard solution;* C_U is the concentration, in mg per mL, of fosphenytoin sodium in the *Test solution;* r_i and r_S are the peak responses for each impurity obtained from the *Test solution;* and r_S is the peak response for phenytoin obtained from the *Standard solution:* and the *Standard solution,* respectively: not more than 0.2% of phenytoin is found; not more than 1.5% of phenytoin related compound B is found; not more than 0.2% of 2,2-diphenylglycine is found; and not more than 2.0% of total impurities is found.~~

Related compounds—

Buffer solution, Mobile phase, Standard stock solution 1, Standard stock solution 2, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Procedure—Inject a volume (about 40 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentages of phenytoin, ~~2,2-diphenylglycine,~~ phenytoin related compound A, phenytoin related compound B, and unknown impurities in each mL of Injection taken by the formula:

$$200{,}000(C/VL)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of the respective impurity in the *Standard solution; V* is the volume, in mL, of the Injection taken to prepare the *Test solution; L* is the labeled amount, in mg per mL, of fosphenytoin sodium in the Injection; and r_i and r_S are the individual peak responses of the impurities in the chromatograms obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.5% of phenytoin related compound B is found; not more than 0.2% of phenytoin is found; not more than 0.2% of ~~2,2-diphenylglycine~~ phenytoin related compound A is found; not more than 0.1% of any individual unknown impurity is found; and not more than 2.0% total impurities is found. [NOTE—Use the peak area and concentration of the USP Phenytoin RS in the *Standard solution* as r_S and C, respectively, to calculate the percentage of the unknown impurities.]

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

~~*Buffer solution* and *Mobile phase*—Proceed as directed in the *Assay* under *Fosphenytoin Sodium.*~~

~~*System suitability solution*—Dissolve an accurately weighed quantity of USP Fosphenytoin Sodium RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.15 mg per mL.~~

~~*Buffer solution*—Dissolve 8.2 g of monobasic potassium phosphate in 900 mL of water. Adjust with 6 N potassium hydroxide solution to a pH of 6.5, dilute with water to 1000 mL, and mix.~~

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~~*Mobile phase*—Prepare a filtered and degassed mixture of *Buffer solution*, methanol, and acetonitrile (73:25:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*System suitability solution*—Dissolve an accurately weighed quantity of USP Fosphenytoin Sodium RS in *Buffer solution,* and dilute quantitatively, and stepwise if necessary, with *Buffer solution* to obtain a solution having a known concentration of about 0.75 mg per mL *(Solution A).* Dissolve accurately weighed quantities of USP Phenytoin RS, 2,2-diphenylglycine, and USP Phenytoin Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having known concentrations of about 0.075, 0.075, and 0.015 mg per mL, respectively *(Solution B).* Transfer 10.0 mL of *Solution A* and 5.0 mL of *Solution B* to a 50-mL volumetric flask, dilute with *Buffer solution* to volume, and mix.~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Fosphenytoin Sodium RS in *Buffer solution,* and dilute quantitatively, and stepwise if necessary, with *Buffer solution* to obtain a solution having a known concentration of about 0.15 mg per mL.~~

~~*Assay preparation*—Transfer an accurately measured volume of Injection, equivalent to about 300 mg of fosphenytoin sodium, to a 200-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 5 mL of this solution to a 50-mL volumetric flask, dilute with *Buffer solution* to volume, and mix.~~

~~*Chromatographic system*—Proceed as directed in the *Assay* under *Fosphenytoin Sodium,* except to inject the *System suitability solution.* The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L11. The flow rate is about 1.0 mL 1.25 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.3 for phenytoin related compound B, 0.5 for 2,2-diphenylglycine, 1.0 for fosphenytoin, and 3.8 for phenytoin; the resolution, *R,* between phenytoin related compound B and 2,2-diphenylglycine is not less than 4.0; the column efficiency is not less than 2250 theoretical plates determined from the fosphenytoin peak; the tailing factor is not more than 1.8; and the relative standard deviation for replicate injections is not more than 1.0% determined from the fosphenytoin peak.~~

~~*Procedure*—Separately inject equal volumes (about 20 µL 40 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of fosphenytoin sodium ($C_{16}H_{12}N_2Na_2O_6P$) in each mL of the Injection taken by the formula:~~

~~$$2000(C/V)(r_U/r_S),$$~~

~~in which C is the concentration, in mg per mL, of USP Fosphenytoin Sodium RS in the *Standard preparation; V* is the volume, in mL, of Injection taken to prepare the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

Buffer solution—Dissolve about 8.2 g of monobasic potassium phosphate in 1 liter of water. Adjust with 6 N potassium hydroxide solution to a pH of 6.5 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution,* methanol, and acetonitrile (73:25:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution 1—Dissolve an accurately weighed quantity of USP Fosphenytoin Sodium RS in methanol, and dilute quantitatively, and stepwise if necessary, with *Buffer solution* to obtain a solution having a known concentration of about 0.75 mg per mL.

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Standard stock solution 2—Dissolve an accurately weighed quantity of USP Phenytoin RS, ~~2,2-diphenylglycine,~~ USP Phenytoin Related Compound A RS, and USP Phenytoin Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.0075 mg per mL, 0.0075 mg per mL, and 0.015 mg per mL, respectively.

Standard preparation—Transfer 10.0 mL of *Standard stock solution 1* and 5.0 mL of *Standard stock solution 2* to a 50-mL volumetric flask. Dilute with *Buffer solution* to volume, and mix.

Assay preparation—Transfer an accurately measured volume of the Injection, equivalent to about 300 mg of fosphenytoin, to a 200-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask. Dilute with *Buffer solution* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 15-cm column that contains packing L11. The flow rate is about 1.25 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.3 for phenytoin related compound B, about 0.5 for ~~2,2-diphenylglycine,~~ phenytoin related compound A, 1.0 for fosphenytoin, and about 3.8 for phenytoin; the resolution, *R*, between phenytoin related compound B and ~~2,2-diphenylglycine~~ phenytoin related compound A is not less than 4.0; the column efficiency is not less than 2250 theoretical plates for the fosphenytoin peak; the tailing factor is not more than 1.8 for the fosphenytoin peak; and the relative standard deviation for replicate injections is not more than 1.0% for the fosphenytoin peak and not more than 5.0% for the phenytoin related compound B, ~~2,2-diphenylglycine,~~ phenytoin related compound A, and phenytoin peaks.

Procedure—Separately inject equal volumes (about 40 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak areas for the fosphenytoin peaks. Calculate the quantity, in mg, of fosphenytoin sodium ($C_{16}H_{13}N_2Na_2O_6P$) in each mL of Injection taken by the formula:

$$2000(C/V)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Fosphenytoin Sodium RS in the *Standard preparation; V* is the volume, in mL, of the Injection taken to prepare the *Assay preparation;* and r_U and r_S are the fosphenytoin peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Fructose, *USP 26* page 834—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-14

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

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Change to read:
USP Reference standards ⟨11⟩—*USP Fructose RS.*

■*USP Endotoxin RS.* ■2S (*USP27*)

Add the following:

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

BRIEFING

Furosemide, *USP 26* page 837—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-15

Change to read:
Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°. ■2S (*USP27*)

Add the following:

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

Change to read:
USP Reference standards ⟨11⟩—*USP Furosemide RS. USP Furosemide Related Compound A RS. USP Furosemide Related Compound B RS.*

■*USP Endotoxin RS.* ■2S (*USP27*)

Add the following:

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

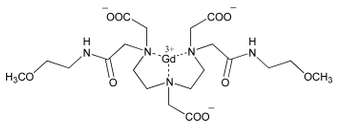
BRIEFING

Gadoversetamide, page 410 of *PF* 29(2) [Mar.–Apr. 2003]. This proposed new monograph is being presented again with revisions recommended by the innovator firm. Also, it is proposed to add storage conditions to the *Packaging and storage* section, in accordance with PSD guidelines.

(RMI: A. Wilk) RTS—39978-1

Add the following:

■Gadoversetamide



$C_{20}H_{34}GdN_5O_{10}$ 661.76

(Gadoversetamide) ~~Gadolinium,~~ [8,11-bis(carboxymethyl)-14-[2-[(2-methoxyethyl)amino]-2-oxoethyl]-6-oxo-2-oxa-5,8,11,14-tetraazahexadecan-16-oato(3-)], gadolinium.

[*N*,*N*-Bis[2-[(carboxymethyl)[[2-methoxyethyl)carbamoyl]methyl]amino]ethyl]glycinato(3-)]gadolinium [*131069-91-5*].

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» Gadoversetamide contains not less than 97.0 percent and not more than 102.0 percent of $C_{20}H_{34}GdN_5O_{10}$, calculated on an anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Gadoversetamide RS. USP Gadoversetamide Related Compound A RS. USP ~~Gadoversetamide~~ Gadodiamide Related Compound B RS.*

Identification—

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

B: The lanthanide selectivity test detects gadolinium (III) in 0.1 N nitric acid with arsenazo (III). Prepare 1.5×10^{-4} M arsenazo (III) ~~acid~~ solution by dissolving 30 mg of arsenazo (III) and 160 mg of urea in 100 mL water, adding 1.6 mL of nitric acid, and diluting with water to 250 mL. Add 10 mg of Gadoversetamide to 1.0 mL of the 1.5×10^{-4} M arsenazo (III) solution, and mix. The color changes from a wine red to green-blue, indicating the presence of gadolinium.

Bacterial endotoxins ⟨85⟩: not more than 15 USP Endotoxin Units per g of gadoversetamide.

Water, *Method Ia* ⟨921⟩: not more than 10.0% (w/w), a solvent mixture of methanol and formamide (9:1) being used.

Limits of free gadolinium (III) and total chelatable material—

MES buffer—~~Transfer 97.6 g of 2-morpholinoethanesulfonic acid (MES) to a 1000-mL volumetric flask, dilute with water to volume, about 950 mL, and mix. Adjust with 20% sodium hydroxide to a pH of 6, dilute with water to volume, and mix.~~ Dissolve 97.6 g of 2-morpholinoethanesulfonic acid (MES) in about 950 mL of water, and mix. Adjust with 20% sodium hydroxide to a pH of 6, dilute with water to 1000 mL, and mix.

Edetate titrant: ~~Pipet 100 mL of 0.02 M edetate disodium VS into a 1000-mL volumetric flask, dilute with water to volume, and mix.~~ 0.002 M edetate disodium VS.

0.003 M Gadolinium (III) titrant—Transfer 0.790 g of gadolinium chloride to a 1000-mL volumetric flask, dilute with ~~0.1 N hydrochloric acid~~ water to volume, and mix.

Test solution—Transfer about 5 g of Gadoversetamide, accurately weighed, into a 250-mL flask, and add 20 mL of water and 2 mL of hydrochloric acid. Stir, and heat to boiling. Rinse the sides of the flask with water. Add 50 mL of *MES buffer* and 100 to 150 µL of xylenol orange TS to impart a light yellow color. Heat to boiling, adjust with ammonium hydroxide to a pH of ~~6.0,~~ 6, and continue boiling for 2 minutes. If the solution is yellow, proceed as directed under *Uncomplexed chelatable material.* If the color is red-violet, proceed as directed under *Free gadolinium (III).*

~~*Blank solution*—Combine 20 mL of water and 2 mL of hydrochloric acid in a 250-mL flask. Heat to boiling with stirring. Rinse the sides of the flask with water, and add 50 mL of *MES buffer* and 100 to 150 µL of xylenol orange TS to impart a slight yellow color to the blank solution. Re-heat to boiling, and adjust with ammonium hydroxide to a pH of 6.0. Continue boiling for 2 minutes, and note the color. If the solution is yellow, proceed as directed below for *Uncomplexed chelatable material.* If the color is red-violet, proceed as directed below for *Free gadolinium (III).*~~

Uncomplexed chelatable material—Continue boiling, and titrate with *0.003 M Gadolinium (III) titrant* to a red-violet endpoint that undergoes no further color change upon addition of more titrant. Record the volume of titrant used to reach the endpoint.

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Free gadolinium (III)—Continue boiling and titrate with *Edetate titrant* to ~~an orange-red~~ a yellow or yellow-orange endpoint that undergoes no further color change upon addition of more titrant. Record the volume of titrant used to reach the endpoint.

Calculations—If the *Test solution* ~~and the *Blank solution* were both~~ was titrated with *Edetate titrant,* calculate the percentage of *Free gadolinium (III)* in the portion of Gadoversetamide taken by the formula:

~~$(66.16/W)(V_{EU} - V_{EB})(M_E)$,~~

$$(66.18/W)(V_{EU})(M_E),$$

in which W is the weight, in g, of Gadoversetamide taken; V_{EU} ~~and V_{EB} are the volumes,~~ is the volume, in mL, of *Edetate titrant* used to titrate the *Test solution;* ~~and the *Blank solution,* respectively;~~ and M_E is the molarity of the *Edetate titrant.* If the sample ~~and blank were both~~ was titrated with *0.003 M Gadolinium (III) titrant,* calculate the percentage of *Uncomplexed chelatable material* in the portion of Gadoversetamide taken by the formula:

~~$(66.16/W)(V_{GU} - V_{GB})(M_G)$,~~

~~$(66.18/W)(V_{GU}) - (M_G)$,~~

$$(66.18/W)(V_{GU})(M_G),$$

in which W is as defined herein; V_{GU} ~~and V_{GB} are the volumes~~ is the volume, in mL, of *0.003 M Gadolinium (III) titrant* used to titrate the *Test solution:* ~~and the *Blank solution,* respectively;~~ and M_G is the molarity of the *0.003 M Gadolinium (III) titrant.* ~~If the *Test solution* was titrated with *Edetate titrant* and the *Blank solution* titrated with *0.003 M Gadolinium (III) titrant,* calculate the percentage of free gadolinium (III) in the portion of Gadoversetamide taken by the formula:~~

~~$(66.16/W)[(V_{EU}M_E) - (V_{GB}M_G)]$,~~

~~in which W, V_{EU}, M_E, V_{GB} and M_G are as defined herein. If the *Test solution* was titrated with *0.003 M Gadolinium (III) titrant* and the *Blank solution* was titrated with *Edetate titrant,* calculate the percentage of free gadolinium (III) in the portion of Gadoversetamide taken by the formula:~~

~~$(66.16/W)[(V_{GU}M_G) - (V_{EB}M_E)]$,~~

~~in which W, V_{GU}, M_G, V_{EB}, and M_E are as defined herein.~~ Not more than 0.05% of free gadolinium III and not more than 0.1% of uncomplexed chelatable material, both calculated on the anydrous basis, are found.

Limit of 2-methoxyethylamine—

Mobile phase—~~Transfer~~ Add 2 mL of 5 M phosphoric acid to ~~a 1000-mL volumetric flask. Add~~ 550 mL of water, mix, and adjust with 10% (w/w) ammonium hydroxide to a pH of 5.0. Add 450 mL of acetonitrile, mix, filter, and degas.

0.4 M Borate buffer—~~Place~~ Add 12.4 g of boric acid ~~into a 1000-mL volumetric flask, add~~ to 300 mL of water, and swirl to suspend. Add 100 mL of 1 N potassium hydroxide, and mix. Adjust with about 60 mL of 1 N potassium hydroxide to a pH of 10.0, dilute with water to 500 mL, and mix. Test the pH, and adjust if necessary.

o-Phthalaldehyde reagent—Dissolve 25 mg of *o*-phthalaldehyde in 0.75 mL of methanol, add 25 mL of *0.4 M Borate buffer* having a pH of 10.0 and 25 µL of 2-mercaptoethanol, and mix. [NOTE—Protect from light. Discard after 3 days.]

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Standard solutions—Prepare aqueous solutions of 2-methoxyethylamine having known concentrations of about 1, 20, and 50 µg per mL, respectively. Derivatize by adding an equal volume of *o-Phthalaldehyde reagent* to each solution immediately before injection.

Test solution—Transfer about 250 mg of Gadoversetamide, accurately weighed, to a 5-mL volumetric flask, and dissolve in and dilute with water to volume. Derivatize the solution by ~~adding 5 mL of *o-Phthalaldehyde reagent.*~~ combining equal volumes of *o-Phthalaldehyde reagent* and *Test solution* immediately before injection.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 335-nm detector and a 250-mm × 4.6-mm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard solutions,* and record the chromatograms as directed for *Procedure:* the relative retention times of *o*-phthalaldehyde and 2-methoxyethylamine are about 0.6 and 1.0, respectively. Plot the concentration of 2-methoxyethylamine in each *Standard solution* versus its peak area, and perform a regression analysis to obtain a slope and an intercept. The correlation coefficient, *r,* is not less than 0.995, and the relative standard deviation for replicate injections of the 50 µg per mL *Standard solution* is not more than 5%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Test solution* and the *Standard solutions* into the chromatograph, record the chromatograms, and measure the peak responses. Determine the concentration, in µg per mL, of 2-methoxyethylamine in the *Test solution* from the standard response line. Calculate the percentage of 2-methoxyethylamine by the formula:

$$0.5C/W,$$

in which C is the concentration, in µg per mL, of 2-methoxyethylamine obtained from the Standard response line; and W is the weight, in mg, of Gadoversetamide taken. Not more than 0.10% (w/w) of 2-methoxyethylamine is present, calculated on the anhydrous basis.

Limit of residual solvents—

Internal standard solution—~~Use butyl alcohol.~~ Dilute butyl alcohol with water (3:5000).

Standard solutions—~~Pipet 25, 100, 250, and 500 µL of isopropyl alcohol, each into a separate 5-mL volumetric flask. Add 1.0 µL of *Internal standard solution* to each of the four flasks, dilute with water to volume, and mix. The resulting four *Standard solutions* contain about 5, 20, 50, and 100 µg of isopropyl alcohol per mL. Pipet 25, 100, 250, and 500 µL of acetonitrile, each into a separate 5-mL volumetric flask. Add 1.0 µL of *Internal standard solution* to each of the four flasks,~~ To four separate 5-mL volumetric flasks, transfer the following designated compositions:

Flask	Isopropyl alcohol	Acetonitrile	Internal standard
1	25 µg	25 µg	1.0 mL
2	100 µg	100 µg	1.0 mL
3	250 µg	250 µg	1.0 mL
4	500 µg	500 µg	1.0 mL

Dilute each flask with water to volume, and mix. The resulting *Standard solutions* contain about 5, 20, 50, and 100 µg of isopropyl alcohol and acetonitrile per mL.

Test solution—Transfer about 500 mg of Gadoversetamide, accurately weighed, to a 5-mL volumetric flask. Add ~~1.0 µL~~ 1.0 mL of *Internal standard solution,* dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × ~~20-m~~ 30-m capillary column

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with a 1.0-µm thickness of phase G35. Helium is used as the carrier gas at a flow rate of about 5 mL per minute. The column temperature is maintained at 35° for five minutes, then is increased at a rate of 15° per minute to 110°. The injection port temperature is maintained at 150°, and the detector temperature is maintained at 300°. Chromatograph the *Standard solutions,* and record the peak ~~responses~~ area ratios as directed for *Procedure:* the relative retention times are about ~~0.55~~ 0.5 for isopropyl alcohol, ~~0.77~~ 0.7 for acetonitrile, and 1.0 for butyl alcohol. Plot the concentration for each standard versus its peak area ratio, and perform a regression analysis. The correlation coefficient, *r,* is not less than 0.995 for each analyte; and the relative standard deviation for replicate injections of the 100 µg per mL *Standard solution* is not more than 5%.

Procedure—Separately inject equal volumes (about 2 µL) of the *Test solution* and the *Standard solutions* into the chromatograph, record the chromatograms, and measure the peak ~~responses.~~ area ratios of the standard peak to the internal standard peak. Determine the concentration of isopropyl alcohol and acetonitrile from the respective standard response lines. Calculate the percentage (w/w) of each solvent in the portion of Gadoversetamide taken by the formula:

$$0.5C/W,$$

in which C is the concentration, in µg per mL, (obtained from the respective standard response line) of isopropyl alcohol and acetonitrile in the *Test solution;* and W is the weight (anhydrous), in mg, of the portion of Gadoversetamide taken: not more than 0.1% (w/w) of isopropyl alcohol is found; and not more than 0.025% (w/w) of acetonitrile is found. The total residual solvent content (sum of the %w/w isopropyl alcohol and of %w/w acetonitrile) does not exceed 0.1% w/w.

Related compounds—

Solution A—~~Transfer about~~ Dissolve 2.06 g of monobasic potassium phosphate and 18.6 mL of 20% w/w tetraethylammonium hydroxide in ~~a 1000-mL volumetric flask, and dilute with water to~~ 950 mL of water. Adjust with phosphoric acid to a pH of 7, dilute with water to ~~volume,~~ make 1000 mL, mix, filter, and degas.

Solution B: ~~acetonitrile.~~ Prepare a filtered and degassed mixture of *Solution A* and acetonitrile (475:25).

Mobile phase—~~Transfer about 2.06 g of monobasic potassium phosphate, 18.6 mL of 20% tetraethylammonium hydroxide, and 1.5 mL of acetonitrile to a 1000-mL volumetric flask, dilute with water to volume, and mix. Adjust with phosphoric acid to a pH of 7, filter, and degas.~~ Use a mixture of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Stock standard solution—Transfer about 50 mg each of USP Gadoversetamide Related Compound A RS and USP ~~Gadoversetamide~~ Gadodiamide Related Compound B RS, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix. [NOTE—The solution may be stored for a week.]

Standard solutions—Prepare aqueous solutions of diluted *Stock standard solution* containing about 25, 150, and 250 µg of each Reference Standard per mL.

Test solution—Transfer about 250 mg of Gadoversetamide, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a metal-free 4.6- × 150-mm column that contains 5-µm packing L1. The flow rate is 1 mL per minute. The chromatograph is programmed to pump a mixture of *Solution A* to *Solution B* ~~having a ratio of 99.85:0.15, respectively.~~ (97:3). ~~Proceed as directed in the *Assay,* except that~~ The

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column is maintained at about 25°. The relative retention times are about ~~0.8~~ 0.6 for ~~gadoversetamide~~ gadodiamide related compound B and ~~1.0~~ 0.7 for gadoversetamide related compound A; the resolution, *R,* between ~~gadoversetamide~~ gadodiamide related compound B and gadoversetamide related compound A is not less than 1.0; and the relative standard deviation for replicate injections is not more than 5% for the 250 µg per mL *Standard solution.*

Procedure—Separately inject equal volumes (about 50 µL) of the *Test solution* and the *Standard solutions* into the chromatograph. Allow 1 hour between injections to remove slow-eluting impurities. Determine the quantities, in ~~mg~~ µg per mL, of gadoversetamide related compound A and ~~gadoversetamide~~ gadodiamide related compound B from the respective Standard response lines. Calculate the percentage of gadoversetamide related compound A in the portion of Gadoversetamide taken by the formula:

$$100C/V,$$

in which C is the concentration of gadoversetamide related compound A, in µg per mL, obtained from the Standard response line; and V is the concentration of gadoversetamide, in µg per mL, in the *Test solution.* Not more than 1.0% (w/w) of gadoversetamide related compound A is found, calculated on the anhydrous basis. Calculate the percentage of ~~gadoversetamide~~ gadodiamide related compound B in the portion of Gadoversetamide taken by the following formula:

$$92.2C/V,$$

in which C is the concentration of ~~gadoversetamide~~ gadodiamide related compound B, in µg per mL, obtained from the Standard response line; and V is as described herein. Not more than 0.5% (w/w) of ~~gadoversetamide~~ gadodiamide related compound B is found, calculated on the anhydrous basis.

Assay—

Mobile phase—~~Transfer~~ Dissolve ~~15 mL of acetonitrile and~~ 1.5 g of boric acid ~~to a 1000-mL volumetric flask, dissolve in and dilute with water to volume,~~ in about 950 mL of water, and mix. Adjust with ammonium hydroxide to a pH of 6.8, add 15 mL of acetonitrile, dilute with water to ~~volume,~~ make 1000 mL, mix, filter, and degas.

Standard preparations—Prepare solutions of USP Gadoversetamide RS in *Mobile phase* having known concentrations of about 1.2, 1.0, and 0.8 mg per mL.

Assay preparation—Transfer about 100 mg of Gadoversetamide, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a metal-free 4.6- × 250-mm column that contains 5-µm packing L1. The column temperature is maintained at about 50°. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparations,* and record the peak responses as directed for *Procedure.* Plot the concentration of each Standard versus its peak area and perform a regression analysis to obtain a slope and intercept for the Standard response line. The correlation coefficient, *r,* is not less than 0.995; and the relative standard deviation for replicate injections of the 1.0 mg per mL *Standard preparation* is not more than 2%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Assay preparation* and *Standard preparations* into the chromatograph, record the chromatograms, and measure the area of the gadoversetamide peak. Determine the quantity, in mg per mL, of gadoversetamide from the Standard response line. Calculate the quantity, in % (w/w), of $C_{20}H_{34}GdN_5O_{10}$ in the portion of Gadoversetamide taken by the formula:

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$$10{,}000C/W,$$

in which C is the concentration, in mg per mL, obtained from the Standard response line, and W is the weight (anhydrous), in mg, of the portion of Gadoversetamide taken to prepare the *Assay preparation.* ■2S (*USP27*)

BRIEFING

Gallamine Triethiodide, *USP 26* page 846—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-15

Change to read:

Packaging and storage—Preserve in tight containers, protected from light.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Gallamine Triethiodide RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Glycopyrrolate, *USP 26* page 869—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-13

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Glycopyrrolate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Chorionic Gonadotropin, *USP 26* page 873; **Chorionic Gonadotropin for Injection,** *USP 26* page 874; **Menotropins,** *USP 26* page 1148; **Menotropins for Injection,** *USP 26* page 1149. One of the reference standards specified in the *Chorionic Gonadotropin, Chorionic Gonadotropin for Injection, Menotropins,* and *Menotropins for Injection* monographs is USP Chorionic Gonadotropin RS. The name of this reference standard is being changed in the monographs to USP Human Chorionic Gonadotropin RS.

(BNT: I. DeVeau) RTS—40191-1

Change to read:

USP Reference standards ⟨11⟩— ~~*USP Chorionic Gonadotropin RS.*~~

■*USP Human Chorionic Gonadotropin RS.*■2S (*USP27*)
USP Endotoxin RS.

Change to read:

Assay—

Standard preparation—Dissolve a suitable quantity of ~~USP Chorionic Gonadotropin RS~~

■USP Human Chorionic Gonadotropin RS.■2S (*USP27*) in a diluent consisting of saline TS, freshly prepared to contain 1 mg per mL of bovine serum albumin and adjusted with sodium hydroxide TS to a pH between 6.9 and 8.0, to obtain a solution having a known concentration of 10 USP Chorionic Gonadotropin Units in each mL. Using the same diluent, prepare three *Standard solutions* such that the respective concentrations of chorionic gonadotropin constitute a geometric series such as 1:1.2:1.44 or 1:2:4 and such that the activity in each mL lies within the range of 0.1 to 1.0 Unit.

Assay preparation—Following the procedure outlined for the *Standard preparation,* prepare solutions of Chorionic Gonadotropin to give three *Test solutions* corresponding to those of the standard.

The animals—Select 20- to 23-day-old female rats, but restrict the selection so that no rat is more than 30% heavier than the lightest. House the animals under uniform conditions of temperature, lighting, feeding, and watering. Mark the animals for identification, and divide them at random into groups of the same number but not less than 10 animals. Assign one group to each of the three *Standard solutions* and three *Test solutions,* respectively.

Procedure—Inject each rat subcutaneously in the dorsal area with 0.20 mL of the solution to which it was assigned, at approximately the same time on each of three consecutive days. On the afternoon of the fifth day, sacrifice the animals, and excise the uterus from each animal by cutting through the cervix, stripping off the surrounding tissue, and severing at the utero-tubal junction. Gently press out the uterine fluid on moistened absorbent paper, and weigh the uterus to the nearest 0.2 mg, using a suitable balance.

Calculation—Tabulate the observed uterine weight for each rat, designated by the symbol *y,* for each dosage group of *f* rats. Proceed as directed in the *Assay* under *Corticotropin Injection,* beginning with "If the data from one or more rats." Compute the log confidence interval *L* (see *Confidence Intervals for Individual Assay* ⟨111⟩). If the confidence interval is more than 0.1938, which corresponds at $P = 0.95$ to confidence limits of 80% and 125% of the computed potency, repeat the assay until the combined data of two or more assays, redetermined as described under *Combination of Independent Assays* ⟨111⟩, meet this limit.

BRIEFING

Chorionic Gonadotropin for Injection, *USP 26* page 874—See briefing under *Chorionic Gonadotropin*.

(BNT: I. DeVeau) RTS—40191-2

Change to read:

USP Reference standards ⟨11⟩— ~~*USP Chorionic Gonadotropin RS.*~~

■*USP Human Chorionic Gonadotropin RS.*■2S (*USP27*)
USP Endotoxin RS.

BRIEFING

Haloperidol, *USP 26* page 893. It is proposed to modify the *Melting range* for this drug substance to more closely reflect the data obtained from the marketed product.

(PA3: S. Salado) RTS—40058-1; 40127-1; 40128-1

Change to read:

Melting range ⟨741⟩: between ~~147° and 152°,~~

■149° and 155°,■2S (*USP27*) determined after drying in vacuum at 60° for 3 hours.

BRIEFING

Histamine Phosphate, *USP 26* page 902—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-14

Change to read:

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

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■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Hyaluronidase Injection, *USP 26* page 906; **Hyaluronidase for Injection,** *USP 26* page 906. It is proposed to revise the *USP Reference standards* section to change the name of USP Tyrosine RS to USP L-Tyrosine RS.

(GTB: I. DeVeau) RTS—40186-2

Change to read:

USP Reference standards ⟨11⟩—*USP Hyaluronidase RS.* ~~*USP Tyrosine RS.*~~

■*USP L-Tyrosine RS.*■2S (*USP27*)
USP Endotoxin RS.

BRIEFING

Hyaluronidase for Injection, *USP 26* page 906—See briefing under *Hyaluronidase Injection*.

(GTB: I. DeVeau) RTS—40186-1

Change to read:

USP Reference standards ⟨11⟩—*USP Hyaluronidase RS.* ~~*USP Tyrosine RS.*~~

■*USP L-Tyrosine RS.*■2S (*USP27*)
USP Endotoxin RS.

Change to read:

Limit of tyrosine—Dissolve the entire contents of 1 or more containers of Hyaluronidase for Injection in sufficient water, accurately measured, to give a concentration of about 60 USP Hyaluronidase Units per mL. Transfer 2.0 mL of the solution to a 15-mL centrifuge tube calibrated at 6 mL, and evaporate at 105° to dryness. Add 200 µL of 6 N sodium hydroxide, and heat with steam under pressure at 121° for 3 hours. Add 300 µL of 7 N sulfuric acid, then add 1.5 mL of water and 1.5 mL of a 15 in 100 solution of mercuric sulfate in 5 N sulfuric acid. Heat on a steam bath for 10 minutes, and cool to room temperature. Add 1 mL of 7 N sulfuric acid and 1 mL of sodium nitrite solution (1 in 500), with shaking. Add water to make 6 mL, mix, centrifuge, and decant the supernatant. Twenty minutes after diluting to 6 mL, determine the absorbance of the supernatant at 540 nm, with a suitable spectrophotometer.

Repeat the preceding test, using the same quantities of the same reagents and in the same manner but omitting the Hyaluronidase for Injection and replacing the 1.5 mL of water with 1.5 mL of a solution of ~~USP Tyrosine RS~~

■USP L-Tyrosine RS■2S (*USP27*)
in 0.4 N sulfuric acid containing 30 µg in each mL.

Calculate the quantity, in µg, of tyrosine in the 2-mL aliquot of the solution of Hyaluronidase for Injection taken by the formula:

$$45(A_U/A_S),$$

in which A_U and A_S are the absorbances of the solution from Hyaluronidase for Injection and the Standard solution, respectively: not more than 0.25 µg of tyrosine is found for each USP Hyaluronidase Unit.

BRIEFING

Hydralazine Hydrochloride, *USP 26* page 907—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-16

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Hydralazine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Hydrocortisone, *USP 26* page 913 and page 2969 of the *First Supplement*—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-11

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Hydrocortisone RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Hydroxyprogesterone Caproate, *USP 26* page 933—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-12

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Hydroxyprogesterone Caproate is sterile, it meets the requirements for *Sterility* under *Hydroxyprogesterone Caproate Injection.*■2S (*USP27*)

BRIEFING

Hyoscyamine Sulfate, *USP 26* page 941—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-15

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Hyoscyamine Sulfate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Inamrinone, *USP 26* page 958. See briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-17

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Inamrinone RS. USP Inamrinone Related Compound A RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Inulin, *USP 26* page 980. On the basis of comments received, it is proposed to revise the test for *Sulfate* so that it conforms to the test specified in general chapter *Chloride and Sulfate* ⟨221⟩, with a limit of 500 ppm.

(PA5: A. Wilk) RTS—39613-1

Change to read:

pH, Chloride, ~~Sulfate,~~

■■2S (*USP27*)

Iron, and Reducing sugars—Dissolve 10.0 g in 20 mL of boiling water in a 100-mL volumetric flask, allow to cool, dilute with water to volume, and mix. Use the solution for the following tests.

pH ⟨791⟩—The pH of the solution is between 4.5 and 7.0.

Chloride ⟨221⟩—A 10-mL portion of the solution shows no more chloride than corresponds to 0.20 mL of 0.020 N hydrochloric acid (0.014%).

~~*Sulfate*—To 10 mL of the solution add 1 mL of barium chloride TS: no turbidity is produced.~~

■■2S (*USP27*)

Iron—To 10 mL of the solution add 0.5 mL of hydrochloric acid and 3 drops of potassium ferrocyanide TS: the solution does not become blue within 1 minute.

Reducing sugars—To 2 mL of the solution add 5 mL of alkaline cupric tartrate TS: no reduction occurs at room temperature, and only slight reduction occurs after one minute of boiling.

Add the following:

■**Sulfate** ⟨221⟩—A 1.0 g portion shows no more sulfate than corresponds to 0.5 mL of 0.020 N sulfuric acid (0.05%). [NOTE—Inulin should be dissolved in 30 to 40 mL of water with gentle warming, prior to dilution to final volume.]■2S (*USP27*)

BRIEFING

Iohexol, *USP 26* page 996. Based on the comments received, it is proposed to rephrase the purity requirements in the *Related compounds* section.

(RMI: A. Wilk) RTS—39887-1

Change to read:

Related compounds—

Solution A: acetonitrile.

Solution B: water.

Mobile phase—Use variable mixtures of a degassed mixture of *Solution A* and *Solution B* as directed for *Chromatographic system.*

System suitability solution—Dissolve accurately weighed quantities of USP Iohexol RS, USP Iohexol Related Compound A RS, and USP Iohexol Related Compound C RS in water to obtain a solution having known concentrations of about 1.5, 0.0075, and 0.0069 mg per mL, respectively.

Test solution—Transfer 75.0 mg of Iohexol, accurately weighed, to a 50-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm stainless steel column that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed to provide variable mixtures of *Solution A* and *Solution B:* the percentage of *Solution A* increases from 1% to 13% at an increase rate of 0.2% per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the retention time for the *O*-alkylated compounds is between 1.1 and 1.4 relative to 1.0 for the *exo*-isomer of iohexol; the resolution, *R,* between iohexol related compound A and iohexol related compound C is not less than 20.0; and the peak area of iohexol related compound C is 0.5% ± 0.1% by comparison to the total area of all of the peaks in the chromatogram.

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of *O*-alkylated compounds

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■and any other individual impurity peak, excluding peaks with a retention time between 0.84 relative to the *endo*-isomer of iohexol (first main peak) and the *endo*-isomer of iohexol,■2S (*USP27*)
in the portion of Iohexol taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the response of each impurity; and r_s is the sum of the responses of all of the peaks: not more than 0.1% of any individual impurity is found; not more than 0.6% *O*-alkylated compounds is found; and the sum of all impurities,

■other than *O*-alkylated compounds,■2S (*USP27*)
is not more than 0.3%.

Add the following:

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

BRIEFING

Isoproterenol Hydrochloride, *USP 26* page 1029—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-16

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Isoproterenol Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

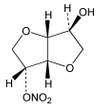
BRIEFING

Diluted Isosorbide Mononitrate, page 829 of *PF* 29(3) [May–June 2003]. This new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision*.

(PA5: A. Wilk) RTS—39903-1

Add the following:

■Diluted Isosorbide Mononitrate



$C_6H_9NO_6$ 191.14

D-Glucitol, 1,4:3,6-dianhydro-, 5-nitrate.

1,4:3,6-Dianhydro-D-glucitol 5-nitrate [*16051-77-7*].

» Diluted Isosorbide Mononitrate is a dry mixture of isosorbide mononitrate ($C_6H_9NO_6$) with lactose or other suitable excipients to permit safe

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handling. It contains not less than 87.5 percent and not more than 92.5 percent (w/w) of isosorbide mononitrate ($C_6H_9NO_6$).

Packaging and storage—Preserve in tight containers. Store at a temperature between 20° and 30°.

USP Reference standards ⟨11⟩—*USP Diluted Isosorbide Dinitrate RS. USP Isosorbide RS. USP Isosorbide Mononitrate RS. USP Isosorbide Mononitrate Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

pH ⟨791⟩: between 4.8 and 6.5. To prepare the test solution, dissolve 5.6 g of Diluted Isosorbide Mononitrate in 50 mL of boiling water, sonicate for 5 minutes, and allow to cool to room temperature.

Water, *Method I* ⟨921⟩: between 0.4% and 0.8%. Proceed as directed for hygroscopic materials. To 1.0 g of sample, accurately weighed, add 5 mL of methanol, shake for 30 minutes, and centrifuge at about 2500 rpm for 5 minutes. Use 1.0 mL of the resulting supernatant.

Residue on ignition ⟨281⟩: not more than 0.1%. [*Caution—Material is explosive upon heating; digest the sample thoroughly before ignition.*]

Heavy metals, *Method I* ⟨231⟩: not more than 10 µg per g.

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Related compounds—

TEST 1—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Standard solution 1—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.0125 mg of isosorbide per mL.

Standard solution 2—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.025 mg of isosorbide per mL.

Standard solution 3—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with absolute alcohol to obtain a solution having a known concentration of about 0.05 mg of isosorbide per mL.

Test solution—Transfer a portion of Diluted Isosorbide Mononitrate, equivalent to about 200 mg of isosorbide mononitrate, accurately weighed, to a suitable container, add 20.0 mL of absolute alcohol, sonicate for 10 minutes, and then centrifuge. Use the supernatant.

Application volume: 20 µL.

Developing solvent system: a mixture of absolute alcohol and toluene (8:2).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. After developing, dry the plate with warm air for about 10 minutes, dip the plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at 105° for 5 minutes. Any spot in the chromatogram obtained from the *Test solution* and corresponding to the R_F value of

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the spots obtained from the *Standard solutions* is not more intense than the spot in the chromatogram obtained from *Standard solution 3:* not more than 0.5% of any individual impurity is found. If the spot in the chromatogram obtained from the *Test solution* is nearly as intense as the spot obtained from *Standard solution 3,* further dilute the *Test solution* (1:1) with absolute alcohol, repeat the test, and compare the intensity of the isosorbide spot in the diluted *Test solution* with the intensity of the spots obtained from the *Standard solutions,* correcting the percent level for the additional dilution of the *Test solution.*

TEST 2—

Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Isosorbide mononitrate related compound A standard solution—Prepare as directed for *Isosorbide mononitrate related compound A standard preparation* in the *Assay.*

Isosorbide dinitrate standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, sonicate and warm if necessary, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.125 mg of isosorbide dinitrate per mL.

Standard solution—Transfer a quantity of USP Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, quantitatively add a volume of *Isosorbide mononitrate related compound A standard solution* and a volume of *Isosorbide dinitrate standard stock solution,* and dilute with water to volume to obtain a solution having a known concentration of about 2.0 mg of USP Isosorbide Mononitrate RS per mL, 0.005 mg of isosorbide mononitrate related compound A per mL, and 0.005 mg of isosorbide dinitrate per mL. Filter a portion of the solution, discarding the first few mL of the filtrate.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of isosorbide mononitrate related compound A and isosorbide dinitrate relative to the amount of isosorbide mononitrate in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$5556(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of the appropriate Reference Standard, USP Isosorbide Mononitrate Related Compound A RS or USP Diluted Isosorbide Dinitrate RS, in the *Standard solution; W* is the weight, in mg, of Diluted Isosorbide Mononitrate used to prepare the *Test solution;* and r_U and r_S are the peak areas of the corresponding components obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.25% of isosorbide mononitrate related compound A is found; and not more than 0.25% of isosorbide dinitrate is found. Calculate the percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$100(r_i/r_s),$$

in which r_i is the peak area for each other impurity obtained from the *Test solution,* and r_s is the sum of the areas of all the peaks: not more than 0.5% of total impurities is found including isosorbide mononitrate related compound A and isosorbide dinitrate; and not more than 0.5% of total impurities is found, the results for *Test 1* and *Test 2* being considered.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (95:5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer an accurately weighed quantity of USP Isosorbide Mononitrate RS to a suitable volumetric flask, dissolve in water, add a volume of methanol equivalent to 4% of the flask volume, and dilute with water to volume to obtain a solution having a known concentration of about 2.0 mg per mL.

Isosorbide mononitrate related compound A standard preparation—Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 1.0 mg per mL. Quantitatively dilute a portion of this solution with water to obtain a solution having a known concentration of about 0.05 mg per mL.

Resolution solution—Transfer 10.0 mL of *Isosorbide mononitrate related compound A standard preparation,* 1.0 mL of *Standard preparation,* and 4.0 mL of methanol to a 100-mL volumetric flask, and dilute with water to volume. Filter a portion of the solution, discarding the first few mL of the filtrate.

Assay preparation—Transfer about 110 mg of Diluted Isosorbide Mononitrate, accurately weighed, to a 50-mL volumetric flask, dissolve in about 25 mL of water, add 2 mL of methanol, dilute with water to volume, and mix. Filter a portion of the solution, discarding the first few mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4-mm × 12.5-cm column that contains packing L1. The flow rate is about 1.5 mL per minute, increasing to 3.0 mL per minute at about 8.5 minutes to ensure that the isosorbide mononitrate peak has completely eluted. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for isosorbide mononitrate related compound A, 1.0 for isosorbide mononitrate, and 4.1 for isosorbide dinitrate; and the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the isosorbide mononitrate peaks. Calculate the quantity, in mg, of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Diluted Isosorbide Mononitrate taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP27*)

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BRIEFING

Isosorbide Mononitrate Tablets, page 936 of *PF* 28(3) [May–June 2002]. This new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision* with the addition of storage instructions added to the *Packaging and storage* section similar to those in the *Diluted Isosorbide Mononitrate* monograph.

(PA5: A. Wilk) RTS—39903-2

Add the following:

■Isosorbide Mononitrate Tablets

» Isosorbide Mononitrate Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$).

Packaging and storage—Preserve in tight containers. Store at a temperature between 20° and 30°.

USP Reference standards ⟨11⟩—*USP Diluted Isosorbide Dinitrate RS. USP Isosorbide Mononitrate RS. USP Isosorbide Mononitrate Related Compound A RS. USP Isosorbide RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 120 mg of isosorbide mononitrate, to a suitable container, add 50.0 mL of absolute alcohol, sonicate for 10 minutes, and then centrifuge. Quantitatively dilute the supernatant (10 in 50) with absolute alcohol.

Standard solution: 0.5 mg USP Isosorbide Mononitrate RS per mL in absolute alcohol.

Application volume: 20 µL.

Developing solvent system: a mixture of chloroform and methanol (95:5).

Spray reagent: Dissolve 1 g of soluble starch in 100 mL of boiling water. Cool, add 0.5 g of potassium iodide, and mix to dissolve.

Procedure—Examine the plate under short-wave UV light, marking any observed spots. Visualize nitrates on the plate by spraying with *Spray reagent* and illuminating with short-wave UV light for about 10 minutes. Isosorbide mononitrate and other nitrates appear as a violet spot on a white to light violet background.

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

Dissolution ⟨711⟩—[To come.]

Uniformity of dosage units ⟨905⟩: meet the requirements for *Content Uniformity.*

Related compounds—

TEST 1—

Adsorbent, Standard solution 1, Standard solution 2, Standard solution 3, Application volume, and *Developing solvent system*—Prepare as directed in *Related compounds, Test 1* under *Diluted Isosorbide Mononitrate.*

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of isosorbide mononitrate, to a suitable container, add 20.0 mL of absolute alcohol, sonicate for 10 minutes, and then centrifuge. Use the supernatant.

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. After developing, dry the plate with warm air for about 10 minutes, dip the plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in

500 mL of water (prepared fresh for each plate), and heat at 105° for 5 minutes. Any spot in the chromatogram obtained from the *Test solution* and corresponding to the R_F value of the spots obtained from the *Standard solutions* is not more intense than the spot in the chromatogram obtained from *Standard solution 3:* not more than 1.0% of any individual impurity is found. If the spot in the chromatogram obtained from the *Test solution* is nearly as intense as the spot obtained from *Standard solution 3,* further dilute the *Test solution* (1:1) with absolute alcohol, repeat the test, and compare the intensity of the isosorbide spot in the diluted *Test solution* with the intensity of the spots obtained from the *Standard solutions,* correcting the percent level for the additional dilution of the *Test solution.*

TEST 2—

Mobile phase and *Resolution solution*—Proceed as directed in the *Assay.*

Isosorbide mononitrate related compound A standard stock solution—Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg of isosorbide mononitrate related compound A per mL.

Isosorbide dinitrate standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.1 mg of isosorbide dinitrate per mL.

Standard solution—Transfer a quantity of USP Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, quantitatively add a volume of *Isosorbide mononitrate related compound A standard stock solution* and a volume of *Isosorbide dinitrate standard stock solution,* and dilute with water to volume to obtain a solution having a known concentration of about 0.1 mg of USP Isosorbide Mononitrate RS per mL, 0.0005 mg of isosorbide mononitrate related compound A per mL, and 0.0005 mg of isosorbide dinitrate per mL. Filter a portion of the solution, discarding the first few mL of the filtrate.

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10% for the isosorbide mononitrate related compound A and isosorbide dinitrate peaks.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Compare the peak areas of the corresponding impurity obtained from the *Test solution* and the *Standard solution,* respectively. The average peak area of the impurity in the *Test solution* is less than or equal to the average peak area of the corresponding peak in the *Standard solution:* not more than 0.5% of isosorbide mononitrate related compound A is found; and not more than 0.5% of isosorbide dinitrate is found.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (7:3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Resolution solution—Prepare a solution of USP Isosorbide Mononitrate RS and USP Isosorbide Mononitrate Related Compound A RS having a concentration of 0.0005 mg of each per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.1 mg per mL. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of isosorbide mononitrate, to a 200-mL volumetric flask, add 100 mL of water, and sonicate for about 10 minutes. Dilute with water to volume, and mix. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Tablets taken by the formula:

$$200C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Isosorbide Mononitrate Extended-Release Tablets, page 832 of *PF* 29(3) [May–June 2003]. This new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision*.

(PA5: A. Wilk) RTS—39903-3

Add the following:

■Isosorbide Mononitrate Extended-Release Tablets

» Isosorbide Mononitrate Extended-Release Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of isosorbide mononitrate ($C_6H_9NO_6$).

Packaging and storage—Preserve in tight containers. Store at a temperature between 20° and 30°.

Labeling—[To come.]

USP Reference standards ⟨11⟩—*USP Diluted Isosorbide Dinitrate RS. USP Isosorbide RS. USP Isosorbide Mononitrate RS. USP Isosorbide Mononitrate Related Compound A RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—Proceed as directed for *Identification* test *A* under *Isosorbide Mononitrate Tablets.*

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

Drug release ⟨724⟩—[To come.]

Uniformity of dosage units ⟨905⟩: meet the requirements for *Content Uniformity.* Proceed as directed in the *Assay,* except to use one Tablet in place of the portion of powdered tablets used in the *Assay preparation.*

~~**Water,** *Method I* ⟨921⟩: not more than 5.0%.~~

~~*Test solution*—Weigh and finely powder 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to one Tablet, accurately weighed, to a suitable container. Add 5.0 mL of methanol, shake for 45 minutes, and then centrifuge at about 4000 rpm for 10 minutes. Use 0.25 mL of the resulting supernatant, correcting for the blank.~~

Related compounds—

TEST 1—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Standard solution 1—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.0125 mg of isosorbide per mL.

Standard solution 2—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.025 mg of isosorbide per mL.

Standard solution 3—Weigh accurately a quantity of USP Isosorbide RS, and dilute quantitatively, and stepwise if necessary, with acetonitrile to obtain a solution having a known concentration of about 0.05 mg of isosorbide per mL.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of isosorbide mononitrate to a suitable flask containing 20.0 mL of acetonitrile. Sonicate for 10 minutes, and then centrifuge. Use the supernatant.

Application volume: 20 µL.

Developing solvent system: a mixture of toluene, ethyl acetate, and isopropyl alcohol (53:32:15).

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. After developing, dry the plate with warm air for about 10 minutes, dip the plate in a solution prepared by dissolving 1.25 g of potassium permanganate and 10.0 g of sodium hydroxide in 500 mL of water (prepared fresh for each plate), and heat at 105° for 5 minutes. Any spot in the chromatogram obtained from the *Test solution* and corresponding to the R_F value of the spots obtained from the *Standard solutions* is not more intense than the spot in the chromatogram obtained from *Standard solution 3:* not more than 1% of any individual impurity is found. [NOTE—The R_F values of isosorbide and isosorbide mononitrate are about 0.2 and 0.6, respectively.] If the spot in the chromatogram obtained from the *Test solution* is nearly as intense as the spot obtained from *Standard solution 3,* further dilute the *Test solution* (1:1) with acetonitrile, repeat the test, and compare the intensity of the isosorbide spot in the diluted *Test solution* with the intensity of the spots obtained from the *Standard solutions,* correcting the percent level for the additional dilution of the *Test solution.*

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TEST 2—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (75:25). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Isosorbide mononitrate related compound A standard stock solution—Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.3 mg per mL.

Isosorbide dinitrate standard stock solution—Dissolve an accurately weighed quantity of USP Diluted Isosorbide Dinitrate RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of about 0.15 mg of isosorbide dinitrate per mL.

Standard stock solution—Transfer 2.0 mL of *Isosorbide mononitrate related compound A standard stock solution* and 4.0 mL of *Isosorbide dinitrate standard stock solution* to a 100-mL volumetric flask. Dilute with water to volume, and mix.

Standard solution—Transfer about 24 mg of USP Isosorbide Mononitrate RS, accurately weighed, to a 100-mL volumetric flask, add 10.0 mL of *Standard stock solution*, add 20 mL of methanol, and dilute with water to volume.

Resolution solution—Transfer 10.0 mL of *Standard stock solution* and 20 mL of methanol to a 100-mL volumetric flask. Dilute with water to volume, and mix.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of isosorbide mononitrate, to a 50-mL volumetric flask, add 40 mL of methanol, and sonicate for about 30 minutes with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 minutes. Quantitatively dilute the supernatant (10 in 50) with water. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R*, between the isosorbide mononitrate related compound A and the isosorbide mononitrate is not less than 1.0. [NOTE—The relative retention times are about 0.9 for isosorbide mononitrate related compound A, 1.0 for isosorbide mononitrate, and 5.6 for isosorbide dinitrate.] Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10% for the isosorbide mononitrate related compound A and isosorbide dinitrate peaks.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of isosorbide mononitrate related compound A and isosorbide dinitrate in the portion of Tablets taken by the formula:

$$25(C/W)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of the appropriate Standard, USP Isosorbide Mononitrate Related Compound A RS or USP Diluted Isosorbide Dinitrate RS, in the *Standard solution; W* is the weight, in mg, of isosorbide mononitrate in the sample used to prepare the *Test solution;* and r_U and r_S are the peak areas of the corresponding component obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.25% of isosorbide mononitrate related compound A is found; and not more than 0.25% of isosorbide dinitrate is found. Calculate the

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percentage of each other impurity (other than isosorbide mononitrate related compound A or isosorbide dinitrate) in the portion of Tablets taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak area for each other impurity obtained from the *Test solution,* and r_s is the sum of the areas of all the peaks: not more than 0.25% of total other impurities is found and not more than 0.5% of total impurities is found, including isosorbide mononitrate related compound A and isosorbide dinitrate.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of water and methanol (8:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Isosorbide mononitrate related compound A standard preparation—Dissolve an accurately weighed quantity of USP Isosorbide Mononitrate Related Compound A RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.15 mg per mL.

Resolution solution—Transfer a quantity of USP Isosorbide Mononitrate RS, accurately weighed, equivalent to about 30 mg of isosorbide mononitrate, to a 250-mL volumetric flask. Dissolve in water, add 10.0 mL of *Isosorbide mononitrate related compound A standard preparation,* add 50 mL of methanol, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a concentration of about 0.12 mg of isosorbide mononitrate per mL and about 0.006 mg of isosorbide mononitrate related compound A per mL.

Standard preparation—Transfer a quantity of USP Isosorbide Mononitrate RS, accurately weighed, to a suitable volumetric flask. Dissolve in water, add a portion of methanol equivalent to about 20% of the flask volume, and dilute with water to volume to obtain a solution having a known concentration of about 0.12 mg of isosorbide mononitrate per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of isosorbide mononitrate, to a 100-mL volumetric flask, add 50 mL of methanol, and sonicate for about 30 minutes with cooling. Warm to ambient temperature, dilute with methanol to volume, and mix. Centrifuge at about 3000 rpm for 10 minutes. Quantitatively dilute the supernatant (10 in 50) with water. Pass a portion of this solution through a filter having a 0.45-µm or finer porosity, and use the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4-mm × 12.5-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between isosorbide mononitrate related compound A and isosorbide mononitrate is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of isosorbide mononitrate ($C_6H_9NO_6$) in the portion of Tablets taken by the formula:

$$500C(r_U / r_S),$$

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in which *C* is the concentration, in mg per mL, of isosorbide mononitrate in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

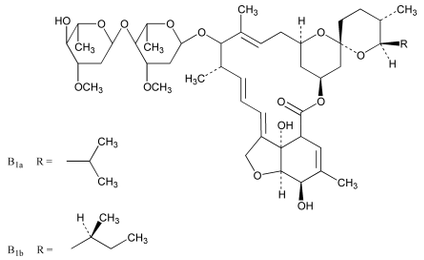
BRIEFING

Ivermectin, page 1135 of *PF* 28(4) [July–Aug. 2002]. On the basis of comments received, it is proposed to revise the specifications for *Related compounds* by giving more explicit limits for the impurities.

(VET: I. DeVeau) RTS—39719-1

Add the following:

■Ivermectin



$C_{48}H_{74}O_{14}$ (Component ~~B_{1a}~~ H_2B_{1a}) 875.10

$C_{47}H_{72}O_{14}$ (Component ~~B_{1b}~~ H_2B_{1b}) 861.07

~~Component B_{1a}: Avermectin A_{1a}, 5-*O*-22,23-dihydro-5-*O*-demethyl-22,23-dihydroavermectin A_{1a}~~ [~~*70161-11-4*~~].

~~Component B_{1b}: Avermectin A_{1b}, 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)avermectin A_{1b}~~ [~~*70209-81-3*~~].

~~Ivermectin~~ [~~*70288-86-7*~~].

Component H_2B_{1a}:

Avermectin A_{1a}, 5-*O*-demethyl-22,23-dihydro-.

(2a*E*,4*E*,8*E*)-(5′*S*,6*S*,6′*R*,7*S*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-6′-(*S*)-*sec*-Butyl-3′,4′,5′,6,6′,7,10,11,14,15,17a,20,20a,20b-tetradecahydro-20,20b-dihydroxy[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside [*70161-11-4*].

Component H_2B_{1b}:

Avermectin A_{1a}, 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-.

(2a*E*,4*E*,8*E*)-(5′*S*,6*S*,6′*R*,7*S*,11*R*,13*R*,15*S*,17a*R*,20*R*,20a*R*,20b*S*)-3′,4′,5′,6,6′,7,10,11,-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′[2*H*]pyran]-7-yl 2,6-dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside [*70209-81-3*].

~~» Ivermectin is a mixture of 5-*O*-demethyl-22,23-dihydroavermectin A_{1a} (component B_{1a}) and 5-*O*-demethyl-25-de(1-methylpropyl)-22, 23-dihydro-25-(1-methylethyl)avermectin A_{1b} (component B_{1b}). It contains not less than 95.0 percent of component B_{1b} plus component B_{1a}, calculated on the water-, ethanol-alcohol-, and formamide-free basis.~~

» Ivermectin is a mixture of Avermectin A_{1a}, 5-*O*-demethyl-22,23-dihydro-(component H_2B_{1a}) and Avermectin A_{1a}, 5-*O*-demethyl-25-de(1-methylpropyl)-22,23-dihydro-25-(1-methylethyl)-(component H_2B_{1b}). It contains not less than 90.0 percent of component H_2B_{1a}, and the

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sum of component H_2B_{1a} plus component H_2B_{1b} is not less than 95.0 percent and not more than 100.5 percent, calculated on the anhydrous and alcohol- and formamide-free basis. It may contain ~~a~~ small amounts of suitable antioxidant and chelating agents.

Packaging and storage—Preserve in tight containers.

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

USP Reference standards ⟨11⟩—*USP Ivermectin RS.*

Clarity of solution—Transfer 1 g to a 50-mL volumetric flask, dissolve in and dilute with toluene to volume, and mix: the solution is clear.

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

Identification—

A: ~~The chromatogram of the *Assay preparation*, obtained as directed in the *Assay*, exhibits major peaks for component B_{1a} and component B_{1b}, the retention times of which correspond to those exhibited in the chromatogram of the *Standard preparation*, obtained as directed in the *Assay*, and the ratio of component B_{1a} to component B_{1b} is not less than 9.0:1–9.0:1.0.~~ *Infrared Absorption* ⟨197K⟩.

B: ~~*Ultraviolet Absorption* ⟨197U⟩—~~

~~*Solution:* 20 µg per mL.~~

~~*Medium:* methanol. The spectrum exhibits maxima at about 238 nm and 245 nm and a shoulder at about 253 nm, and the absorptivity at the wavelength of maximum absorption at about 245 nm is between 37.2 and 39.2, calculated on the water-, ethanol- alcohol-, and formamide-free basis.~~ The retention times of the component H_2B_{1a} peak and the component H_2B_{1b} peak in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation*, as obtained in the *Assay.*

~~**Clarity and color of solution**—Dissolve 1.0 g of it in toluene to obtain 50 mL of solution: the solution is clear and its absorbance at 440 nm in a 1-cm cell is not more than 0.024, toluene being used as the blank.~~

Specific rotation ⟨781S⟩: between –17° and –20°, ~~determined at 20° and~~ calculated on the water-, ~~ethanol-~~ alcohol-, and formamide-free basis.

Test solution: ~~25~~ 5 mg per mL, in methanol.

Water, *Method I* ⟨921⟩: not more than 1.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Limit of ethanol alcohol and formamide—

~~*Standard solutions*—Transfer 3.0 mL of dehydrated alcohol to a 100 mL volumetric flask, dilute with water to volume, and mix (*Solution A*). Transfer 1.0 mL of formamide to a 100 mL volumetric flask, dilute with water to volume, and mix (*Solution B*). Transfer 3.0 mL of *Solution A* and 3.0 mL of *Solution B* to a 100 mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of ethanol alcohol and formamide of 0.0009 and 0.0003 mL per mL, respectively (*Solution C*). Transfer 8.0 mL of *Solution A* and 8.0 mL of *Solution B* to a 100 mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of ethanol alcohol and formamide of 0.0024 and 0.0008 mL per mL, respectively (*Solution D*). Transfer 4.0 mL of *Solution C* and 4.0~~

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~~mL of *Solution D* to separate 15-mL centrifuge tubes, add 2.0 mL of *m*-xylene to each tube, stopper, mix, centrifuge, and discard the upper *m*-xylene layers. The retained lower layers are *Standard solutions C* and *D*.~~

~~*Test solution*—Transfer 120 mg of Ivermectin, accurately weighed, to a 15-mL centrifuge tube, and dissolve in 2.0 mL of *m*-xylene. Add 2.0 mL of water, mix, and centrifuge. Transfer the *m*-xylene layer to a 15-mL centrifuge tube, and extract again with 2.0 mL of water. Discard the *m*-xylene layer, and combine the two aqueous layers to obtain the *Test solution*.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and contains a 1.8-m × 3.2-mm column packed with 80- to 100-mesh support S2. The injection port is maintained at about 190°, and the detector is maintained at about 250°. Helium is used as the carrier gas at a flow rate of about 40 mL per minute. The column is maintained at about 150° for 12 minutes after injection, then raised at a rate of 20° per minute to 180°, and then held for 20 minutes.~~

~~*Procedure*—Separately inject equal volumes (about 2 µL) of *Standard solutions C* and *D* and the *Test solution* into the chromatograph, record the chromatograms, and measure the ethanol-alcohol and formamide peak responses. Plot the peak responses for ethanol alcohol and formamide versus concentrations, in mL per mL, of ethanol alcohol and formamide, respectively, obtained from *Standard solutions C* and *D*. From the graphs so obtained, determine the concentrations of ethanol alcohol and formamide in the *Test solution*.[NOTE—In the event that the peak responses of the *Test solution* are significantly outside the ranges of peak responses obtained with *Standard solutions C* and *D*, prepare additional *Standard solutions*, and chromatograph them to obtain peak responses bracketing those obtained with the *Test solution*.] Calculate the percentages of ethanol alcohol and formamide in the portion of Ivermectin taken by the formula:~~

$$~~400{,}000Cd/W~~,$$

~~in which *C* is the concentration of ethanol alcohol or formamide, in mL per mL, of the *Test solution*, *d* is the density of ethanol alcohol (0.79) or formamide (1.13), and *W* is the weight, in mg, of Ivermectin taken: not more than 5.0% of ethanol alcohol (C_2H_5OH) and 3.0% of formamide are found.~~

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

Standard solution 1—Transfer ~~3.0~~ 2.0 mL of dehydrated alcohol to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solution 2—Transfer 1.0 mL of formamide to a 100-mL volumetric flask, dilute with water to volume, and mix.

Standard solution 3—Transfer 5.0 mL of *Standard solution 1* and 5.0 mL of *Standard solution 2* to a 50-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of formamide and alcohol of 0.001 and ~~0.003~~ 0.002 mL per mL, respectively. Transfer 2.0 mL of this solution to a 15-mL centrifuge tube, add 2.0 mL of *m*-xylene, insert the stopper, mix, and centrifuge. Remove the upper *m*-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of *Internal standard solution*, and mix. Each mL of this solution contains about ~~0.0012~~ 0.0008 mL of alcohol and 0.0004 mL of formamide.

Standard solution 4—Transfer 10.0 mL of *Standard solution 1* and 10.0 mL of *Standard solution 2* to a 50-mL volumetric flask, dilute with water to volume, and mix to obtain a solution having concentrations of alcohol and formamide of ~~0.006~~ 0.004 and 0.002 mL per mL, respectively. Transfer

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2.0 mL of this solution to a 15-mL centrifuge tube, add 2.0 mL of *m*-xylene, insert the stopper, mix, and centrifuge. Remove the upper *m*-xylene layer, and extract it with 2.0 mL of water. Discard the upper layer, combine the two retained lower aqueous layers, add 1.0 mL of *Internal standard solution*, and mix. Each mL of this solution contains about ~~0.0024~~ 0.0016 mL of alcohol and 0.0008 mL of formamide.

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

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

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

$$500{,}000CD/W,$$

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

Related ~~substances~~ compounds~~—Using the chromatogram of the *Assay preparation* obtained as directed in the *Assay*, calculate the percentage of each related substance compound in the Ivermectin taken by the formula:~~

~~$100r_i/r_t$,~~

~~in which r_i is the response of each individual peak, except those of component B_{1a} and component B_{1b}, and r_t is the sum of the responses of all of the peaks in the chromatogram. Not more than 2% of any individual related substance compound is found, and the sum of all related substances is not more than 4%.~~

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

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

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Standard solution 1—Transfer 1.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Standard solution 2—Transfer 5.0 mL of *Standard solution 1* to a 100-mL volumetric flask, dilute with methanol to volume, and mix.

Test solution—Use the *Assay preparation*.

Procedure—Separately inject equal volumes (about 20 µL) of *Standard solution 1*, *Standard solution 2*, and the *Test solution* into the chromatograph, record the chromatogram of the *Test solution* for a period of time equivalent to twice the retention time of the ~~principal~~ main peak in the chromatogram obtained from *Standard solution 1*, and measure the ~~responses for the major peaks. In the chromatogram obtained from the *Test solution*, the area of any peak with a retention time of 1.3 to 1.5 about 1.2 to 1.4, relative to the principal peak, is not greater than twice 2.5 times the area of the principal peak in the chromatogram obtained from *Standard solution 1* (2.0% 2.5%); the area of any other peak, aside from the two principal peaks, is not greater than the area of the principal peak in the chromatogram obtained from *Standard solution 1* (1.0%); and the sum of the areas of all the peaks, apart from the two principal peaks, is not greater than four times the area of the principal peak in the chromatogram obtained from *Standard solution 1* (4.0%) (4%). Disregard any peak with an area less than that of the principal peak in the chromatogram of *Standard solution 2* (0.05%).~~ peak areas. Calculate the percentage of each impurity by the formula:

$$100r_i/(r_s - r_b)$$

in which r_i is the peak area for each individual impurity in the *Test solution* chromatogram; r_s is the sum of all peaks in the *Test solution* chromatogram; and r_b is the total area of all peaks in a blank chromatogram: not more than 2.5% is found for the sum of all peaks with a relative retention time of about 1.3 to 1.4 (corresponding to H_4B_{1a} isomers and $\Delta^{2,3}$ H_2B_{1a}); not more than 1% is found for the peak with a relative retention time of about 0.7 (corresponding to 8a-oxo-H_2B_{1a}); not more than 0.7% is found for the peak with a relative retention time of about 0.5 (corresponding to Avermectin B_{1a}); not more than 0.5% is found for any other individual impurity peak; not more than 1% is found for the sum of all other individual peaks; and not more than 4% is found for the sum of the areas of all the peaks, apart from the two main peaks (H_2B_{1a} and H_2B_{1b}). Disregard any peak with an area less than that of the two main peaks (H_2B_{1a} and H_2B_{1b}) in the chromatogram of *Standard solution 2* (0.05%).

Assay—

~~*Mobile phase*—Prepare a mixture of acetonitrile, methanol, and water (530:350:120), filter through a filter having a porosity of 1 µm or less, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Ivermectin RS quantitatively in *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.~~

~~*Assay preparation*—Transfer about 40 mg of Ivermectin, accurately weighed, to a 100-mL volumetric flask, dissolve in methanol, dilute with *Mobile phase* to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed under *Procedure*: component B_{1b} is eluted at a retention time of about 14 minutes, followed by component B_{1a} at a retention time of about 17 minutes. The resolution, *R*, between the peaks for component B_{1b} and~~

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~~component B_{1a} is not less than 3.0, the column efficiency determined from the component B_{1a} peak is not less than 2000 theoretical plates, the tailing factor for the component B_{1a} peak is not more than 2.5, and the relative standard deviation of the peak responses for component B_{1a} for replicate injections is not more than 1.0%.~~

~~*Procedure*—[NOTE—Use peak areas where peak responses are indicated.] Separately inject equal volumes (about 50 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms over a period of time that is twice the retention time of the peak for component B_{1a}, and measure the peak responses for component B_{1a} and component B_{1b}. Calculate the percentage of component B_{1a} plus component B_{1b} in the portion of Ivermectin taken by the formula:~~

~~$$100(CP/W)(r_U/r_S),$$~~

~~in which C is the concentration, in mg per mL, of USP Ivermectin RS in the *Standard preparation*, P is the designated percentage of the sum of component B_{1a} and component B_{1b} in the USP Ivermectin RS, W is the weight, in mg, of Ivermectin taken to prepare the *Assay preparation*, and r_U and r_S are the sums of the peak responses for component B_{1a} and component B_{1b} obtained from the *Assay preparation* and the *Standard preparation*, respectively.~~

Mobile phase—Prepare a mixture of acetonitrile, methanol, and water (53:35:12), pass through a filter having a 1-µm or finer porosity, and degas. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩). Increasing the proportion of water increases the elution times and allows better separation of impurities.

Standard preparation—Dissolve an accurately weighed quantity of USP Ivermectin RS in methanol to obtain a solution having a known concentration of about 0.8 mg per mL.

Assay preparation—Transfer about 80 mg of Ivermectin, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Sonicate, if necessary.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for component H_2B_{1b} and 1.0 for component H_2B_{1a}; the resolution, R, between component H_2B_{1b} and component H_2B_{1a} is not less than 3.0; the column efficiency determined from the component H_2B_{1a} peak is not less than 5000 theoretical plates; the tailing factor for component H_2B_{1a} peak is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.0% determined from the component H_2B_{1a} peak.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for component H_2B_{1a} and component H_2B_{1b}. Calculate the quantity, in mg, of component H_2B_{1a} ($C_{48}H_{74}O_{14}$) and component H_2B_{1b} ($C_{47}H_{72}O_{14}$) in the portion of Ivermectin taken by the formula:

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of component H_2B_{1a} or component H_2B_{1b} in the *Standard preparation;* and r_U and r_S are the peak responses for component H_2B_{1a} or component H_2B_{1b} obtained from the *Assay preparation* and the *Standard preparation*, respectively. ■2S (*USP27*)

In-Process Revision

BRIEFING

Labetalol Hydrochloride, *USP 26* page 1051—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-18

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Labetalol Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Lidocaine Hydrochloride, *USP 26* page 1078—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-17

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Lovastatin, *USP 26* page 1099. On the basis of the comments and toxicological data received, it is proposed to change the *Limit of Lovastatin related compound A* to 0.5%. This limit is representative of marketed products. In the absence of any significant adverse comment, it is proposed to implement this revision via the *Sixth Interim Revision Announcement* pertaining to *USP 26–NF 21,* with an official date of December 1, 2003.

(PA4: E. Gonikberg) RTS—40148-1

Change to read:

▲**Limit of Lovastatin related compound A—**

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and 0.01 M phosphoric acid (13:7). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Lovastatin RS and USP Lovastatin Related Compound A RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, to obtain a solution containing 2.0 µg of each per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Lovastatin RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 2.0 µg per mL.

Test solution—Transfer about 25 mg of Lovastatin, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 200-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The column temperature is maintained at 40°. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for lovastatin and 1.3 for lovastatin related compound A; and the resolution, *R,* between lovastatin and lovastatin related compound A is not less than 6.0. Chromato-

graph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of lovastatin related compound A in the portion of Lovastatin taken by the formula:

$$2.5F(C/W)(r_U/r_S),$$

in which F is the response factor for lovastatin related compound A and is equal to 1.6; C is the concentration, in µg per mL, of USP Lovastatin RS in the *Standard solution;* W is the weight, in mg, of Lovastatin in the *Test solution;* r_U is the peak response for lovastatin related compound A obtained from the *Test solution;* and r_S is the peak response for lovastatin obtained from the *Standard solution:* not more than ~~0.2%~~

•0.5%•6
of lovastatin related compound A is found.▲*USP26*

BRIEFING

Manganese Chloride, *USP 26* page 1123—See briefing under *Aminophyline.*

(PA1: K. Russo) RTS—40176-18

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Medroxyprogesterone Acetate, *USP 26* page 1139 and page 2974 of the *First Supplement*—See briefing under *Alprostadil.*

(PA1: C. Anthony) RTS—40156-13

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Medroxyprogesterone Acetate is sterile, it meets the requirements for *Sterility* under *Medroxyprogesterone Acetate Injectable Suspension.*■2S (*USP27*)

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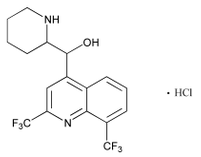
BRIEFING

Mefloquine Hydrochloride. Because there is currently no *USP* monograph for this drug substance, a new monograph is being proposed. The test for *Related compounds* is based on data obtained with a 4.0-mm × 25-cm LiChrospher 100 (Merck) column that contains 5-µm packing L1. Typical retention times are about 2 minutes for quinidine, 4 minutes for mefloquine, 15 minutes for related compound B, and 36 minutes for related compound A.

(PA7b: B. Davani) RTS—38976-1

Add the following:

■Mefloquine Hydrochloride



$C_{17}H_{16}F_6N_2O \cdot HCl$ 414.77

4-Quinolinemethanol, α-2-piperidinyl-2,8-bis(trifluoromethyl)-, monohydrochloride, (*R**,*S**)- (±)-.

DL-*erythro*-α-2-Piperidyl-2,8-bis(trifluoromethyl)-4-quinolinemethanol monohydrochloride [*51773-92-3*].

» Mefloquine Hydrochloride contains not less than 99.0 percent and not more than 101.0 percent of $C_{17}H_{16}F_6N_2O \cdot HCl$, calculated on the anhydrous basis.

Packaging and storage—Preserve in tight, light-resistant containers. Store between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Mefloquine Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It responds to the tests for *Chloride* ⟨191⟩.

Specific rotation ⟨781⟩: between –0.2° and +0.2°. Use a solution prepared by dissolving about 2.5 g in methanol, and dilute with methanol to 50.0 mL.

Water, *Method I* ⟨921⟩: not more than 3.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Related compounds—

Mobile phase—Dissolve 1 g of tetraheptylammonium bromide in a mixture of methanol, 1.5 g per L solution of sodium hydrogen sulfate, and acetonitrile (1:2:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 8 mg of USP Mefloquine Hydrochloride RS and 8 mg of quinidine sulfate to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer about 0.10 g of Mefloquine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Diluted test solution—Transfer 1.0 mL of the *Test solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 1.0 mL of this solution to a 20-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector, a 4-mm × 2.5-cm precolumn, and a 4.0-mm × 25-cm column, both containing 5-µm packing L1. The flow rate is about 0.8 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.5

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for quinidine and 1.0 for mefloquine; the resolution, *R,* between the quinidine peak and the mefloquine peak is not less than 8.5; and the relative standard deviation for replicate injections is not more than 3%.

Procedure—Equilibrate the column with *Mobile phase* at a flow rate of about 2 mL per minute for about 30 minutes. Inject 20 µL of *Diluted test solution*. Adjust the sensitivity of the system so that the height of the major peak is at least 50% of the full scale of the recorder. Separately inject equal volumes (about 20 µL) of the *Test solution* and *Diluted test solution* into the chromatograph, record the chromatogram for a time that is 10 times the retention time of the main peak, and measure the responses of all peaks, excluding the main peak and any other peak producing a response of less than 0.2 times (0.02%) of the main peak in chromatogram of the *Diluted test solution*. The response of any peak in the *Test solution* with a relative retention time of about 0.7, with reference to the main peak, is not more than twice the area of the main peak in the chromatogram of the *Diluted test solution* (0.2%). The response of any other individual peak, other than the main peak in the chromatogram of the *Test solution,* is not greater than that of the main peak in the chromatogram of the *Diluted test solution* (0.1%), and the sum of the responses of any such peaks in the chromatogram of *Test solution* is not greater than five times the response of the main peak in the chromatogram of the *Diluted test solution* (0.5%).

Assay—Dissolve about 0.35 g, accurately weighed, in 15 mL of anhydrous formic acid, and add 40 mL of acetic anhydride. Titrate with 0.1 N perchloric acid VS, and determine the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 41.48 mg of $C_{17}H_{16}F_6N_2O \cdot HCl$.■2S *(USP27)*

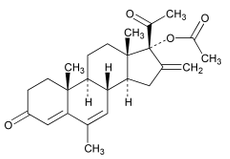
BRIEFING

Melengestrol Acetate. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The test for *Limit of residual solvents* uses gas chromatography with flame-ionization detection based on analyses performed with the Tianjing No. 2 Chemical Reagent Factory GDX-101 brand of 3-mm × 2-m stainless steel column packed with S3 porous, uncoated polymeric beads. The liquid chromatographic procedures in the test for *Related compounds* and in the *Assay* are based on analyses performed with a Waters Symmetry Shield TM RP8 brand of 4.6-mm × 25.0-cm, 5-µm particle size L7 column. Interested parties are encouraged to validate the analytic methods using other chromatographic columns and submit comments to the USP Expert Committee on Veterinary Drugs (Standards).

(VET: I. DeVeau) RTS—39413-1; 39498-1; 39562-1

Add the following:

■Melengestrol Acetate



$C_{25}H_{32}O_4$ 396.52

Pregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-16-methylene-.

17-Hydroxy-6-methyl-16-methylenepregna-4,6-diene-3,20-dione acetate [*2919-66-6*].

» Melengestrol Acetate contains not less than 97.0 percent and not more than 103.0 percent of $C_{25}H_{32}O_4$, calculated on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store at controlled room temperature.

Labeling—Label it to indicate that it is for veterinary use only.

USP Reference standards ⟨11⟩—*USP Melengestrol Acetate RS. USP Melengestrol Acetate Related Compound A RS. USP Melengestrol Acetate Related Compound B RS.*

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Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 10 µg per mL.

Medium: alcohol.

C: The retention time of the melengestrol acetate peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Melting temperature ⟨741⟩: between 219° and 226°.

Specific rotation ⟨781S⟩: between –132.0° and –122.0°, at 20°.

Test solution: 10.0 mg per mL, in chloroform.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 0.5% of its weight.

Heavy metals, *Method II* ⟨231⟩: not more than 0.001%.

Limit of residual solvents—

Standard solution—Separately and accurately transfer 2.5 mL of dehydrated alcohol, 5.5 mL of ethyl acetate, 0.5 mL of dichloromethane, and 0.4 mL of dioxane into a 100-mL volumetric flask. Mix, and dilute with dimethylformamide to volume. Pipet 5 mL of this solution into another 50-mL volumetric flask, mix well, and dilute with dimethylformamide to volume.

Test solution—Weigh accurately about 500 mg of Melengestrol Acetate, and transfer to a 5-mL volumetric flask, add a suitable amount of dimethylformamide, and sonicate for 5 minutes until completely dissolved. Dilute with dimethylformamide to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 2-m stainless steel column packed with S3 porous polymeric beads, 60–80 mesh size. The temperature of the injector port, column, and detector are maintained at 200°, 155°, and 250°, respectively. The carrier gas is nitrogen, flowing at a rate of 60 mL per minute. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the elution order is alcohol, dichloromethane, ethyl acetate, dioxane, and dimethylformamide. The resolution, *R,* between each peak should be not less than 1.5, and the relative standard deviation for five replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 1.0 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas for alcohol, dichloromethane, ethyl acetate, and dioxane. Calculate the concentration of the individual solvents, in ppm, in the portion of Melengestrol Acetate taken by the formula:

$$CV(r_U / r_S)/(1000W),$$

in which C is the concentration, in g per mL, of the relevant solvent in the *Standard solution; V* is the sample volume in mL; r_U and r_S are the peak areas of the relevant solvent obtained from the *Test solution* and the *Standard solution,* respectively; and W is the weight, in mg, of Melengestrol Acetate taken to prepare the *Test solution:* not more than 5000 ppm of alcohol, 5000 ppm of ethyl acetate, 600 ppm of dichloromethane, and 380 ppm of dioxane is found.

Related compounds—

Mobile phase—Prepare a mixture of acetonitrile and water (50:50).

Standard solution—Dissolve an accurately weighed quantity of USP Melengestrol Acetate RS, USP Melengestrol Acetate Related Compound A RS, and USP Melengestrol Acetate Related Compound B RS in methanol to obtain a solution having known concentrations of about 0.005 mg of each per mL.

Test solution—Use the *Assay preparation* prepared as directed in the *Assay.*

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Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a multiwavelength detector set at 240 and 262 nm and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* [NOTE—Melengestrol acetate and melengestrol related compound A will generate larger peak areas at 262 nm than at 240 nm; melengestrol acetate related compound B will generate a larger peak area at 240 nm than at 262 nm] the relative retention times are about 0.77, 1.0, and 1.05 for melengestrol acetate related compound A, melengestrol acetate, and melengestrol acetate related compound B, respectively; the resolution, *R,* between melengestrol acetate related compound A and melengestrol acetate related compound B is not less than 5.0; the column efficiency for the melengestrol acetate related compound A peak is greater than 1500; the tailing factor is less than 2.0; and the relative standard deviation of replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, identify the peaks, and determine which detector wavelength generates the larger peak area for each impurity. Using the larger peak area, calculate the percentage of each impurity in the portion of Melengestrol Acetate taken by the formula:

$$100(C_S / C_U)(r_I / r_S),$$

in which C_S is the concentration, in mg per mL, of either melengestrol related compound A or melengestrol related compound B in the *Standard solution* [NOTE—If using the impurity peak area generated at 262 nm, C_S is the concentration of melengestrol related compound A; if using the impurity peak area generated at 240 nm, C_S is the concentration of melengestrol related compound B]; C_U is the concentration, in mg per mL, of melengestrol acetate in the *Test solution;* r_I is the peak area of each impurity obtained from the *Test solution;* and r_S is the peak area of either melengestrol related compound A or melengestrol related compound B in the *Standard solution* [NOTE—If using the impurity peak area generated at 262 nm, r_S is the peak area of melengestrol related compound A; if using the impurity peak area generated at 240 nm, C_S is the peak area of melengestrol related compound B]: not more than 0.5% of any identified impurity is found; not more than 0.2% of any unidentified impurity is found; and not more than 1.0% of total impurities is found.

Assay—

Mobile phase—Prepare a mixture of acetonitrile and water (50:50).

Standard preparation—Dissolve an accurately weighed quantity of USP Melengestrol Acetate RS in methanol to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Melengestrol Acetate, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with methanol to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 287-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L7. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation* as directed for *Procedure:* the column efficiency is not less than 1500; the tailing factor is not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* in duplicate into the chromatograph, record the chromato-

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grams, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{25}H_{32}O_4$ in the portion of Melengestrol Acetate taken by the formula:

$$2CW(r_U / r_S),$$

in which C is the concentration, in mg per mL, of the *Standard preparation; W* is the weight, in mg, of Melengestrol Acetate used to prepare the *Assay preparation;* r_U is the average peak area of the melengestrol acetate peak obtained from the *Assay preparation;* and r_S is the average peak area of the melengestrol acetate peak obtained from the *Standard preparation.*■2S (*USP27*)

BRIEFING

Menadiol Sodium Diphosphate, *USP 26* page 1145—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-20

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Menadione, *USP 26* page 1146—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-21

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Menadione RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Menotropins, *USP 26* page 1148—See Briefing under *Chorionic Gonadotropin*.

(BNT: I. DeVeau) RTS—40191-3

Change to read:

USP Reference standards ⟨11⟩—*USP Menotropins RS*. ~~*USP Chorionic Gonadotropin RS.*~~

■*USP Human Chorionic Gonadotropin RS.*■2S (*USP27*)
USP Endotoxin RS.

Change to read:

Assay for follicle-stimulating hormone—

Diluting solution—Using the *Diluent* under *Assay for luteinizing hormone,* dissolve an accurately weighed quantity of ~~USP Chorionic Gonadotropin RS~~

■USP Human Chorionic Gonadotropin RS■2S (*USP27*) to contain a concentration of 70 USP Chorionic Gonadotropin Units per mL, readjusting the pH, if necessary, to 7.2 ± 0.2.

Standard preparations—Dissolve an accurately weighed quantity of USP Menotropins RS in the *Diluting solution* to obtain solutions having known concentrations of about 2.5, 5.0, and 10.0 USP Follicle-Stimulating Hormone Units per mL.

Assay preparations—Following the procedure given under the *Standard preparations,* use Menotropins in place of the Reference Standard to obtain similar solutions.

Control solution—Use the *Diluting solution* as the control solution. Store all solutions at 5 ± 3° for the duration of the assay and properly dispose of any unused portions.

Test animals—Select 20- to 21-day old female rats with weights within a 10-g range of each other. Proceed as directed under *Test animals* in the *Assay for luteinizing hormone* beginning with "House the animals..."

Dose determination trial—Use the method described under the *Procedure* to determine a 3-dose range in which the lowest dose produces a definite response in some of the rats in the low-dose group (as compared with the control group) and the highest dose produces a submaximal to maximal response in the high-dose group. Doses must be established in a geometric progression. The normal dose response range will occur between 0.5 and 6.0 USP Follicle-Stimulating Hormone Units total dose per rat. Useful dose ranges will vary with the sensitivity of the rat strain selected.

Procedure—Inject each rat of each group subcutaneously in the dorsal area with 0.2 mL of the solution to which it was assigned. For *Dose determination trial* only, similarly inject each rat in the control group with 0.2 mL of the *Control solution.* Repeat these injections at approximately the same time of day after 24 hours and 48 hours. Twenty-four hours after the last injection, weigh each rat, sacrifice the animals, and carefully dissect out the ovaries of each rat, removing any fat and fibrous tissue. Thoroughly dry the ovaries by pressing against absorbent paper, avoiding damage to follicles on the ovary surface, and immediately weigh them to the nearest 0.2 mg, using a suitable balance.

Calculation—Tabulate the observed ovarian pair weight for each rat designated by the symbol *y,* for each dosage group of *f* rats. For apparently outlying ovarian weight gain, an attempt may be made to correct the organ mass relative to the mass of the rat from which it was taken. For the *y*-value in question, calculate for each of the *f* rats in the appropriate group the ratio of ovarian weight to the total body weight. Reject the *y*-value if its corresponding ratio differs from the rest of the group by more than 1.5 standard deviations. If the data from one or more rats are missing, adjust to groups of equal size by suitable means (see *Replacement of Missing Values* ⟨111⟩). Total the values of *y* in each group, and designate each total as *T,* using subscripts 1 to 3 for the three successive dosage levels and subscripts *S* and *U* for the Standard and the material under test, respectively. Test both the agreement in slope of the dosage-response lines for the Standard and for the material under test, and the lack of curvature as directed for a 3-dose balanced assay (see *Tests of Assay Validity* ⟨111⟩). If the combined discrepancy as measured by F_3 exceeds its tabular value in Table 9 (see *Combination of Independent Assays* ⟨111⟩), regard these data as preliminary, and repeat the assay.

Determine the logarithm of follicle-stimulating hormone potency of the Menotropins taken by the formula:

$$M = (4iT_a / 3T_b) + \log R,$$

in which $T_a = \Sigma(T_U - T_S)$, $T_b = \Sigma(T_3 - T_1)$, i is the interval between successive log doses of both the *Standard preparation* and *Assay preparation,* and $R = v_S/v_U$ is the ratio of the high dose of the Standard in USP Units (v_S) to the high dose of the Menotropins in mg (v_U). Compute the log confidence interval (see *Design and Analysis of Biological Assays* ⟨111⟩).

Replication—Repeat the entire determination at least once. Test the agreement among the two or more independent determinations, and compute the weights/mean log-potency M and its confidence interval, L_C (see *Confidence Intervals for Individual Assays* ⟨111⟩). If this exceeds 0.18, repeat the assay until the confidence interval of the combined results is 0.18 or less.

The potency P_* is satisfactory if P_* = antilog M is not less than 80% and not more than 125% of the labeled potency and if the log confidence interval does not exceed 0.18.

BRIEFING

Menotropins for Injection, *USP 26* page 1149—See briefing under *Chorionic Gonadotropin*.

(BNT: I. DeVeau) RTS—40191-4

Change to read:

USP Reference standards ⟨11⟩—*USP Menotropins RS*. ~~*USP Chorionic Gonadotropin RS.*~~

■*USP Human Chorionic Gonadotropin RS.*■2S (*USP27*)
USP Endotoxin RS.

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BRIEFING

Mepivacaine Hydrochloride, *USP 26* page 1154—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-19

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Mepivacaine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Metaraminol Bitartrate, *USP 26* page 1173—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-22

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Metaraminol Bitartrate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Methohexital, *USP 26* page 1188—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-20

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Methohexital RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Methyldopate Hydrochloride, *USP 26* page 1203—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-23

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Methyldopate Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Methylene Blue, *USP 26* page 1205—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-24

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩——*USP Methylene Blue RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Methylergonovine Maleate, *USP 26* page 1206—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-14

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Methylergonovine Maleate RS*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Methylprednisolone Acetate, *USP 26* page 1211—See briefing under *Alprostadil.*

(PA1: C. Anthony) RTS—40156-15

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Methylprednisolone Acetate is sterile, it meets the requirements for *Sterility* under *Methylprednisolone Acetate Injectable Suspension.*■2S (*USP27*)

BRIEFING

Metoclopramide Hydrochloride, *USP 26* page 1217—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-16

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Metoclopramide Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Metoprolol Tartrate, *USP 26* page 1222—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-25

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Metoprolol Tartrate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

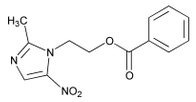
BRIEFING

Metronidazole Benzoate, page 7747 of *PF* 25(2) [Mar.–Apr. 1999]. This new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process Revision*. Storage conditions have been added to the *Packaging and storage* section. Interested parties are encouraged to submit comments.

(PA7b: B. Davani) RTS—40038-1

Add the following:

■Metronidazole Benzoate



$C_{13}H_{13}N_3O_4$ 275.3

2-(2-Methyl-5-nitroimidazol-1-yl)ethyl benzoate [*13182-89-3*].

» Metronidazole Benzoate contains not less than 98.5 percent and not more than 101.0 percent of $C_{13}H_{13}N_3O_4$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed, light-resistant containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Metronidazole Benzoate RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The principal spot in the chromatogram of the *Test solution* corresponds to that in the chromatogram of *Standard solution A,* as obtained in the test for *Related compounds*.

Acidity—Neutralize 40 mL of a mixture of dimethylformamide and water (1:1) with hydrochloric acid or 0.02 M sodium hydroxide, add 0.2 mL of methyl red TS and 2.0 g of Metronidazole Benzoate, mix to dissolve, and titrate with 0.02 M sodium hydroxide: not more than 0.25 mL is required to produce a color change.

Loss on drying ⟨731⟩—Dry it at 80° for 3 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Related compounds—

Adsorbent: 0.2-mm layer of chromatographic silica gel mixture.

Test solution—Transfer about 200 mg of Metronidazole Benzoate, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with acetone to volume, and mix.

Standard solution A—Dissolve an accurately weighed quantity of USP Metronidazole Benzoate RS in acetone, and dilute quantitatively, and stepwise if necessary, with acetone to obtain a solution having a known concentration of about 0.1 mg per mL.

Standard solution B—Transfer 4.0 mL of *Standard solution A* to a 10-mL volumetric flask, dilute with acetone to volume, and mix.

Standard solution C—Transfer about 10 mg each of metronidazole and 2-methyl-5-nitroimidazole, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with acetone to volume, and mix.

Application volume: 10 µL.

Developing solvent system: ethyl acetate.

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Examine the plate under short-wavelength UV light: the test is valid only if the metronidazole and 2-methyl-5-nitroimidazole spots obtained from *Standard solution C* are clearly separated; no spot obtained from the *Test solution* is larger or more intense than the principal spot obtained from *Standard solution A* (0.5%); and not more than three spots, excluding

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the principal spot, obtained from the *Test solution* are larger or more intense than the principal spot obtained from *Standard solution B* (1.0%).

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.

Assay—Transfer about 250 mg of Metronidazole Benzoate, accurately weighed, to a suitable container, and dissolve with stirring in 50.0 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid is equivalent to 27.53 mg of $C_{13}H_{13}N_3O_4$·■2S (*USP27*)

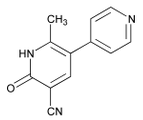
BRIEFING

Milrinone, page 2175 of *PF* 27(2) [Mar.–Apr. 2001]. It is proposed to revise the *Packaging and storage* statement to conform to specifications provided by the manufacturer and to those found in *Preservation, Packaging, Storage, and Labeling* under the *General Notices*.

(PA5: A. Wilk; PSD: C. Okeke) RTS—38978-3

Add the following:

■Milrinone



$C_{12}H_9N_3O$ 211.22

[3,4′-Bipyridine]-5-carbonitrile, 1,6-dihydro-2-methyl-6-oxo-.

1,6-Dihydro-2-methyl-6-oxo[3,4′-bipyridine]-5-carbonitrile [*78415-72-2*].

» Milrinone contains not less than 98.5 percent and not more than 101.5 percent of $C_{12}H_9N_3O$, calculated on the anhydrous basis.

Caution—Milrinone is a cardiotonic agent.

Packaging and storage—Preserve in ~~well-closed, light-resistant containers.~~ tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Milrinone RS. USP Milrinone Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: The retention time of the major peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *Standard solution,* as obtained in the test for *Chromatographic purity.*

Water, *Method I* ⟨921⟩: not more than 2.0%.

Residue on ignition ⟨281⟩: not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Chromatographic purity—

pH 7.5 Phosphate buffer—Dissolve 2.7 g of dibasic potassium phosphate in 800 mL of water, add 2.4 mL of triethylamine, adjust with phosphoric acid to a pH of about 7.5, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *pH 7.5 Phosphate buffer* and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Milrinone RS in *Mobile phase* to obtain a solution having a known concentration of about 2 mg per mL, heat in a water bath at approximately 80°, and/or sonicate, if necessary.

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Standard solution—Dilute an appropriate volume of *Standard stock solution* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of 0.006 mg per mL.

System suitability solution—Dissolve an accurately weighed quantity of USP Milrinone Related Compound A RS in *Mobile phase* to obtain a solution having a known concentration of about ~~2~~ 0.2 mg per mL. Heat in a water bath at approximately 80°, and/or sonicate, if necessary, to dissolve. Transfer ~~1.0~~ 10.0 mL of this solution and 1.0 mL of the *Standard stock solution* to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Transfer about 100 mg of Milrinone, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Heat in a water bath at approximately 80°, if necessary.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.6 for milrinone related compound A and 1.0 for milrinone; the resolution, *R,* between milrinone related compound A and milrinone is not less than 4.0; and the relative standard deviation for replicate injections of milrinone is not more than 5.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Milrinone taken by the formula:

$$5000(C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Milrinone RS in the *Standard solution; W* is the weight, in mg, of milrinone taken to prepare the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response obtained from the *Standard solution:* not more than 0.3% of any individual impurity is found; and not more than 1.0% of total impurities is found.

Organic volatile impurities, *Method V* ⟨467⟩: meets the requirements.

Solvent: dimethyl sulfoxide.

Assay—Transfer about 200 mg of Milrinone, accurately weighed, to a 100-mL beaker, and dissolve by stirring in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid VS is equivalent to 21.12 mg of $C_{12}H_9N_3O$.■2S (*USP27*)

BRIEFING

Nandrolone Decanoate, *USP 26* page 1269—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-16

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Nandrolone Decanoate is sterile, it meets the requirements for *Sterility* under *Nandrolone Decanoate Injection*. ■2S (*USP27*)

In-Process Revision

BRIEFING

Naratriptan Tablets, page 84 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to change the particle size of the column used in the *Assay* to avoid problems with back-pressure. The new column is a Sphereclone Phenyl brand of L11 column. Typically, the retention time of naratriptan is between 4 and 7 minutes. It is proposed to change the size of the filter used for the *Assay preparation* to a size that is routinely used in laboratory work.

(PA3: S. Salado) RTS—39986-1

Add the following:

■Naratriptan Tablets

» Naratriptan Tablets contain an amount of Naratriptan Hydrochloride equivalent to not less than 90.0 percent and not more than 110.0 percent of the labeled amount of naratriptan ($C_{17}H_{25}N_3O_2S$).

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

USP Reference standards ⟨11⟩—*USP Naratriptan Hydrochloride RS. USP Naratriptan Related Compound A RS. USP Naratriptan Related Compound B RS.*

NOTE—When performing assays and tests, store all standard, system suitability, and sample solutions in a cool place, protected from light.

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Diluent—Prepare a mixture of methylene chloride and methanol (1:1).

Adsorbent: high performance thin-layer chromatographic silica gel.

Test solution—Transfer a number of Tablets, equivalent to 5 mg of naratriptan, to a 25-mL flask, add 1.0 mL of water to wet the Tablets, and gently shake to remove the Tablet film coating. Add 4.5 mL of *Diluent,* and shake for 5 minutes or until the Tablets have dispersed. Centrifuge at 3000 rpm for 10 minutes, and pass through a nylon filter having a 0.45-µm porosity.

Developing solvent system: a mixture of methylene chloride, alcohol, and triethylamine (10:2:1).

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

Dissolution ⟨711⟩—

Medium: 0.1 N hydrochloric acid; 500 mL, deaerated.

Apparatus 1: 100 rpm.

Times: 15 minutes.

Procedure—Determine the amount of $C_{17}H_{25}N_3O_2S$ dissolved from the difference between first derivative absorbance values at the wavelengths of maximum and minimum in the range from 226 nm to 236 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Naratriptan Hydrochloride RS in the same *Medium.* [NOTE—Do not sonicate the Standard solution to effect solution. Dissolve the Reference Standard with *Dissolution Medium* at about 37°.]

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{17}H_{25}N_3O_2S$ is dissolved in 15 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Chromatographic purity—

0.05 M Ammonium phosphate buffer and *Resolution solution*—Prepare as directed in the test for *Chromatographic purity* under *Naratriptan Hydrochloride.*

Solution A—Use filtered and degassed *0.05 M Ammonium phosphate buffer.*

Solution B—Use filtered and degassed acetonitrile.

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Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Test solution—Transfer 5 Tablets into a suitable amber flask. Add 20.0 mL of 0.1 N sodium hydroxide, and allow to stand for 10 minutes. Sonicate for 10 minutes with regular vigorous swirling of the flask. Add 30.0 mL of *0.05 M Ammonium phosphate buffer,* and mix well. Centrifuge a portion of this solution at 3500 rpm for about 10 minutes, and pass through a suitable filter having a ~~0.2 µm~~ 0.45-µm porosity, discarding the first 3 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 225-nm detector and a 4.6-mm × 15-cm column that contains ~~4 µm~~ packing L1. The column temperature is maintained at 40°. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–35.0	97→80	3→20	linear gradient
35.0–40.0	80	20	isocratic
40.0–40.1	80→97	20→~~30~~ 3	linear gradient
40.1–50.0	97	3	re-equilibration

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.07 for naratriptan related compound B and 1.0 for naratriptan; and the resolution, *R,* between naratriptan and naratriptan related compound B is not less than 1.5.

Procedure—Inject a volume (equivalent to about 5 µg of naratriptan hydrochloride) of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for all of the peaks. Calculate the percentage of each impurity in the portion of ~~Naratriptan Hydrochloride~~ Tablets taken by the formula:

~~$100Fr_i/(r_N + \Sigma Fr_i)$,~~

$$100(r_i/F)/[r_N + \Sigma(r_i/F)],$$

in which F is the relative response factor (see the accompanying table for values) for each impurity; r_i is the peak response for each impurity; and r_N is the naratriptan peak response (see the accompanying table for limits).

Relative retention time	Relative response factor (F)	Limit (%)
1.07	0.6	0.2
1.26	0.6	0.2
1.33	0.4	0.3
1.44	0.6	0.2
1.62	0.5	0.2

In addition to not exceeding the limits listed in the accompanying table, not more than 0.2% of any other individual impurity is found; and not more than 1.5% of total impurities is found.

Assay—

0.01 M Triethylamine phosphate buffer, Mobile phase, and *Resolution solution*—Prepare as directed in the *Assay* under *Naratriptan Hydrochloride.*

Standard preparation—Dissolve an accurately weighed quantity of USP Naratriptan Hydrochloride RS in 0.1 N sodium hydroxide to obtain a solution having a known concentration of about 0.2 mg per mL. Dilute an accurately

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measured volume of this solution in *0.01 M Triethylamine phosphate buffer* to obtain a solution having a known concentration of about 20 µg per mL.

Assay preparation—Transfer 5 Tablets into an amber 250-mL volumetric flask, add 30 mL of 0.1 N sodium hydroxide, and shake on a wrist-action shaker for at least 30 minutes. Sonicate for 10 minutes with regular vigorous swirling of the flask. Add about 170 mL of *0.01 M Triethylamine phosphate buffer,* and mix well. Allow to cool to room temperature, dilute with *0.01 M Triethylamine phosphate buffer* to volume, and mix. Centrifuge a portion of this solution at 3500 rpm for about 10 minutes, and pass through a suitable filter having a ~~0.2 µm~~ 0.45-µm porosity, discarding the first 3 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 224-nm detector and a 4.6-mm × 15-cm column that contains ~~3 µm~~ 5-µm packing L11. The flow rate is about 1.3 mL per minute. Chromatograph the *Resolution solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for naratriptan related compound A, 1.0 for naratriptan, and 1.1 for naratriptan related compound B; and the resolution, *R,* between naratriptan related compound A and naratriptan and between naratriptan related compound B and naratriptan is not less than 1.5. Chromatograph the *Standard preparation,* record the chromatogram, and measure the peak response as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject volumes (equivalent to about 1 µg of naratriptan hydrochloride) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of naratriptan ($C_{17}H_{25}N_3O_2S$) in the portion of Tablets taken by the formula:

$$(335.47/371.93)100(C/D)(r_U/r_S),$$

in which 335.47 and 371.93 are the molecular weights of naratriptan and naratriptan hydrochloride, respectively; C is the concentration, in mg per mL, of USP Naratriptan Hydrochloride RS in the *Standard preparation; D* is the concentration, in mg per mL, of naratriptan in the *Assay preparation,* based upon the labeled quantity of naratriptan in the portion of Tablets taken and the extent of dilution; and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Nifedipine Extended-Release Tablets, *USP 26* page 1313, page 2986 of the *First Supplement,* and page 87 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to add the description of the sinker used in *Drug release Test 2.*

(BPC: M. Marques) RTS—40129-1

Change to read:

Drug release ⟨724⟩—

Test 1: If the product complies with this test, the labeling indicates that the product meets USP *Drug Release Test 1.*

Medium: water; 50 mL.

Apparatus 7—Do not use the reciprocating disk, but use a 25-cm plexiglas rod, the perimeter of the Tablets being affixed to the rod with a water-insoluble glue. The solution containers are 25-mm test tubes, 150 to 200 mm in length, and the water bath is maintained at 37 ± 0.5°.

Times: 4, 12, and 24 hours.

Diluting solution 1: a mixture of methanol and acetonitrile (1:1).

Diluting solution 2: a mixture of *Diluting solution 1* and water (1:1).

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Standard solutions—Transfer about 50 mg of USP Nifedipine RS, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Diluting solution 1,* dilute with water to volume, and mix to obtain a Standard stock solution. Quantitatively dilute this Standard stock solution ■with *Diluting solution 2*■1S (*USP26*) to obtain solutions having known concentrations of 0.01 mg per mL, 0.05 mg per mL, and 0.20 mg per mL that are used at 4 hours, 12 hours, and 24 hours, respectively.

Procedure—[NOTE—For the 4-hour time period, filter, determine the absorbance at 456 nm, and use this determination to correct for excipient interference at the other time periods.] Determine the amount of $C_{17}H_{18}N_2O_6$ released at each 4-hour interval by employing UV absorption at the wavelength of maximum absorbance at about 338 nm, in 0.5-cm cells. Use test solutions that are suitably diluted, if necessary, with *Diluting solution 1* and water to obtain a final mixture of water, methanol, and acetonitrile (2:1:1) in comparison with the appropriate *Standard solution,* using *Diluting solution 2* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
4	between 5% and 17%
12	between 43% and 80%
24	not less than 80%

Test 2: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Buffer concentrate—Transfer 330.9 g of dibasic sodium phosphate and 38 g of citric acid to a 1-liter volumetric flask, add water to dissolve, add 10 mL of phosphoric acid, dilute with water to volume, and mix.

Medium—Mix 125.0 mL of *Buffer concentrate* and 1 liter of 10% sodium lauryl sulfate solution, and dilute to 10 liters. Adjust if necessary to a pH of 6.8; 900 mL.

Apparatus 2: 50 rpm,

■with sinkers (see *Figure 1*).■2S (*USP27*)

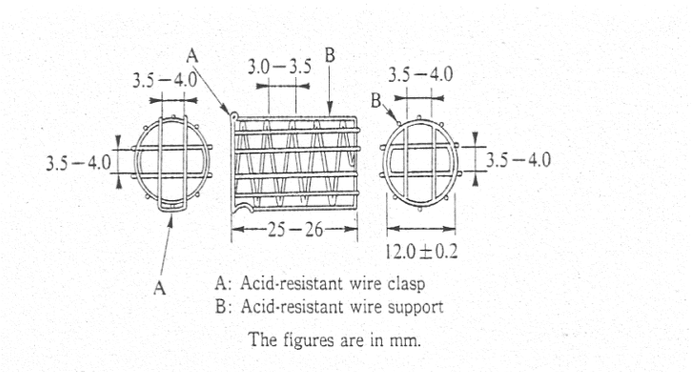

Fig. 1 (printed with permission of the Japanese Pharmacopoeia)

Times: 3, 6, and 12 hours.

Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (70:30). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Nifedipine RS in methanol to obtain a solution having a known concentration of about 1.11 mg per mL. Dilute quantitatively and stepwise with *Dissolution Medium* to obtain a solution having a known concentration of 0.1 mg per mL.

Chromatographic system—The liquid chromatograph is equipped with a 350-nm detector and a 4.0-mm × 125-mm column that contains 3-µm packing L1. The flow rate is about 1.5 mL per minute. The column is maintained at about 40°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 2000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of filtered portions of the *Standard solution* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Determine the amount of nifedipine ($C_{17}H_{18}N_2O_6$) dissolved.

Tolerances—The percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$) released in vivo and dissolved at the times specified conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
3	between 10% and 30%
6	between 40% and 65%
12	not less than 80%

■*Test 3:* If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3.*

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5.

Apparatus 2: 100 rpm.

Time: 1 hour.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Dissolution Medium* for *Phase 2.*] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using the *Dissolution Medium* as the blank.

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Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.034 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Dissolution Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 30% and 55%
8	not less than 60%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE—

Phase 1:

Medium: 0.05 M phosphate buffer, pH 7.5.

Apparatus 2: 100 rpm.

Time: 25 minutes.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—[NOTE—After the run, take the Tablet out of the dissolution vessel, adapt a sinker to it, and transfer the Tablet with the sinker to the dissolution vessel containing the *Dissolution Medium* for *Phase 2*.] Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 1* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Dissolution Medium* as the blank.

Phase 2:

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, 8, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released in *Phase 2* from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Dissolution Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released in vivo and dissolved at the times specified, conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved*
1	not more than 30%
4	between 40% and 70%
8	not less than 70%
12	not less than 80%

* For each dosage unit, add the amount dissolved in phosphate buffer, pH 7.5 from *Phase 1* to the amount dissolved at each time point in *Phase 2*.

Test 4: If the product complies with this test, the labeling indicates that the product meets USP *Drug Release Test 4.*

Medium: 0.5% sodium lauryl sulfate in simulated gastric fluid without enzyme, pH 1.2; 900 mL.

Apparatus 2: 100 rpm.

Times: 1, 4, and 12 hours.

Standard solution—Prepare a solution in *Medium* having an accurately known concentration of about 0.067 mg of USP Nifedipine RS per mL for Tablets labeled to contain 60 mg, and of about 0.034 mg of USP Nifedipine RS per mL for Tablets labeled to contain 30 mg. If necessary, a volume of methanol, not exceeding 10% of the final volume, can be used to help solubilize nifedipine.

Procedure—Determine the amount of $C_{17}H_{18}N_2O_6$ released from UV absorbances at the wavelength of maximum absorbance at about 238 nm using filtered portions of the solution under test, in comparison with the *Standard solution*, using *Dissolution Medium* as the blank.

Tolerances—The cumulative percentages of the labeled amount of nifedipine ($C_{17}H_{18}N_2O_6$), released at the times specified, conform to *Acceptance Table 1.*

FOR TABLETS LABELED TO CONTAIN 30 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 12% and 35%
4	between 44% and 67%
12	not less than 80%

FOR TABLETS LABELED TO CONTAIN 60 MG OF NIFEDIPINE

Time (hours)	Amount dissolved
1	between 10% and 30%
4	between 40% and 63%
12	not less than 80%

■1S (*USP26*)

In-Process Revision

BRIEFING

Nitrofurantoin Capsules, *USP 26* page 1315. A proposal for a new monograph for *Nitrofurantoin Extended-release Capsules* was published in *PF* 24(6) [Nov.–Dec. 1998] and published again with modifications in *PF* 25(5) [Sept.–Oct. 1999]. However FDA informed USP that all *Nitrofurantoin Capsules* currently available on the market are considered by the agency as immediate-release. On the basis of these comments, the USP Expert Committee on Biopharmaceutics decided to withdraw the proposal for a new monograph for *Nitrofurantoin Extended-release Capsules*, and to add a *Dissolution Test 2* in the monograph for *Nitrofurantoin Capsules*.

(BPC: M. Marques) RTS—36856-1; 40091-1; 40101-1

Change to read:

Labeling—Capsules that contain the macrocrystalline form of Nitrofurantoin are so labeled.

■When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.■2S (*USP27*)

Change to read:

Dissolution ⟨711⟩ —

■TEST 1■2S (*USP27*)
(where labeled as containing Nitrofurantoin macrocrystals)—
Medium: pH 7.2 (±0.05) phosphate buffer; 900 mL.
Apparatus 1: 100 rpm.
Times: 1, 3, and 8 hours.
Procedure—Determine the amount of $C_8H_6N_4O_5$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 375 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Nitrofurantoin RS in the same *Medium.*

Tolerances—The percentage of the labeled amount of $C_8H_6N_4O_5$ dissolved at the 1-hour time point conforms to *Acceptance Table 1* under *Drug Release* ⟨724⟩, and the percentages dissolved at the 3- and 8-hour time points conform to the criteria for the final test time in *Acceptance Table 1* under *Drug Release* ⟨724⟩.

Time (hours)	Amount dissolved
1	between 20% and 60%
3	not less than 45%
8	not less than 60%

■TEST 2 (where labeled as containing both Nitrofurantoin macrocrystalline and monohydrate forms). If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

Acid medium: 0.01 N hydrochloric acid or 1 hour; 900 mL.

pH 7.5 Buffer medium—Prepare a pH 7.5 buffer concentrate by dissolving 62.2 g of potassium hydroxide and 129.3 g of monobasic potassium phosphate in water, dilute with water to 1 liter, and mix. After 1 hour change the *Acid medium* to *pH 7.5 Buffer medium* by adding 50 mL of pH 7.5 buffer concentrate, for an additional 6 hours.

Apparatus 2: 100 rpm, with sinkers made of teflon-coated steel wire prepared by forming a coil approximately 22 mm long from a 13-cm length of 20-gauge wire (See *Figure 1*).

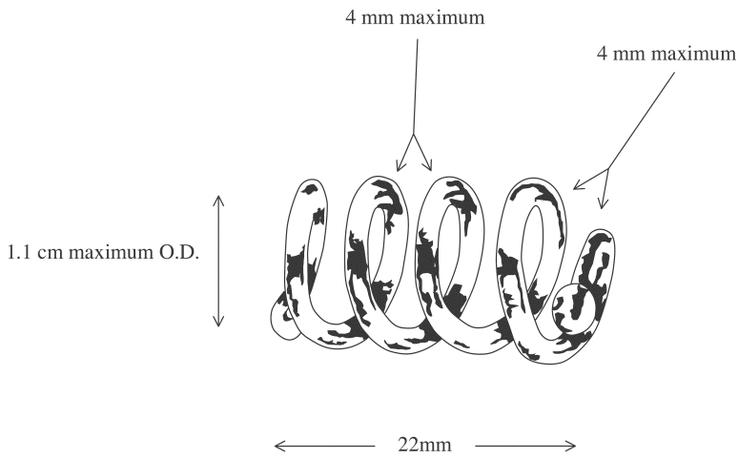


Fig. 1. Sinker.

Times: 1, 3, and 7 hours.

Acid-stage standard solution—Prepare a solution of USP Nitrofurantoin RS in *Acid medium* to obtain a solution having a known concentration of about 0.025 mg per mL.

Buffer-stage standard solution—Prepare a solution of USP Nitrofurantoin RS in *pH 7.5 Buffer medium* to obtain a solution having a known concentration of about 0.075 mg per mL.

Procedure—Determine the amount of $C_8H_6N_4O_5$ dissolved from UV absorbances at the isosbestic wavelength at about 375 nm on filtered portions of each solution under test suitability diluted, if necessary, with *Acid medium* or *pH 7.5 Buffer medium* when appropriate in comparison with the appropriate *Standard solution*.

Tolerances—The percentages of the labeled amount $C_8H_6N_40_5$ dissolved at the specified times conform to the following tables.

Time (hours)	Amount dissolved (individual)	Amount dissolved (mean)
1	between 2% and 16%	between 5% and 13%
3	between 27% and 69%	between 39% and 56%
7	not less than 68%	not less than 81%

Level	Number Tested	Criteria
L1	12	The mean percentage of dissolved label claim lies within the range for the means at each interval and is not less than the stated amount at the final test time. All individual values lie within the ranges for the individuals at each interval and are not less than the stated amount at the final test time.
L2	12	The mean percentage of dissolved label claim lies whithin the range for the means at each interval and is not less than the stated amount at the final test time. Not more than 2 of the 24 individual values, lie outside the stated ranged for individuals at each interval and not more than 2 of 24 is less than the stated amount at the final test time.

■2S (*USP27*)

In-Process Revision

BRIEFING

Diluted Nitroglycerin, *USP 26* page 1319—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-26

Change to read:

Packaging and storage—Preserve in tight, light-resistant containers, and prevent exposure to excessive heat.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Diluted Nitroglycerin RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Norepinephrine Bitartrate, *USP 26* page 1327—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-27

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Norepinephrine Bitartrate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Norgestrel and Ethinyl Estradiol Tablets, *USP 26* page 1338. It is proposed to replace the *Disintegration* test with a *Dissolution* test. The HPLC procedure in the *Dissolution* test was developed using a Hypersil C8 BDS brand of L7 packing. The retention times are about 4.3 minutes for norgestrel and about 3.2 minutes for ethinyl estradiol.

(BPC: M. Marques) RTS—35216-1

Delete the following:

■~~**Disintegration** ⟨701⟩: 15 minutes, the use of disks being omitted.~~■2S (*USP27*)

In-Process Revision

Add the following:

■**Dissolution** ⟨711⟩—

Medium: 0.0005% (w/v) polysorbate 80; 500 mL.

Apparatus 2: 75 rpm.

Time: 60 minutes.

Determine the amount of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$ dissolved by employing the following method. [NOTE—Do not use plastics during the preparation of solutions.]

Mobile phase—Prepare a filtered and degassed mixture of water and acetonitrile (3:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution [NOTE—A volume of alcohol not exceeding 2% of the final volume of the solution may be used to aid in dissolving the Reference Standards.]—Dissolve an accurately weighed quantity of USP Norgestrel RS and USP Ethinyl Estradiol RS in *Dissolution Medium,* and dilute quantitatively, and stepwise if necessary, with *Dissolution Medium* to obtain a solution having known concentrations similar to those expected in the *Test solution*.

Test solution—Use a portion of the solution under test filtered through 0.7-µm borosilicate microfiber filter.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 247-nm detector (for norgestrel analysis), and a spectrofluorometric detector (for ethinyl estradiol analysis) with an excitation wavelength of about 285 nm and an emission wavelength of 310 nm, and a 4.6-mm × 15-cm column that contains packing L7. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for ethinyl estradiol and 1.0 for norgestrel; and the relative standard deviation for replicate injections is not more than 3.0% for the ethinyl estradiol and norgestrel peaks.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantities, in mg, of norgestrel ($C_{21}H_{28}O_2$) and ethinyl estradiol ($C_{20}H_{24}O_2$) dissolved by the formula:

$$(500C)(r_U / r_S),$$

in which C is the concentration, in mg per mL, of the appropriate Reference Standard in the *Standard solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Tolerances—Not less than 75% *(Q)* of the labeled amount of $C_{21}H_{28}O_2$ and $C_{20}H_{24}O_2$ are dissolved in 60 minutes.■2S (*USP27*)

BRIEFING

Ondansetron Hydrochloride, *USP 26* page 1351 and page 92 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to modify *Method I* in the test for *Chromatographic purity* by replacing the USP Ondansetron Related Compound B RS, which is unavailable, with a new Reference Standard that contains a mixture of ondansetron, ondansetron related compound A, and ondansetron related compound B. The proposed change to the limit in the test for *Limit of ondansetron related compound D* is canceled. Other minor changes are intended to better reflect the actual approved material.

(PA3: S. Salado) RTS—39985-1

Change to read:

USP Reference standards ⟨11⟩—*USP Ondansetron Hydrochloride RS. USP Ondansetron Related Compound A RS.* ~~*USP Ondansetron Related Compound B RS*~~

■*USP Ondansetron Resolution Mixture RS.*■2S (*USP27*) *USP Ondansetron Related Compound C RS. USP Ondansetron Related Compound D RS.*

In-Process Revision

Change to read:

Limit of ondansetron related compound D—

Mobile phase—Prepare a filtered and degassed mixture of 0.02 M monobasic potassium phosphate (previously adjusted with 1 M sodium hydroxide to a pH of 5.4) and acetonitrile (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Ondansetron Related Compound D RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.4 µg per mL.

System suitability solution—Dissolve suitable quantities of USP Ondansetron Related Compound D RS and USP Ondansetron Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.6 µg per mL and 1 µg per mL, respectively.

Test solution—Transfer about 50 mg of Ondansetron Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 328-nm detector and a 4.6-mm × 20-cm column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for ondansetron related compound C and 1.0 for ondansetron related compound D; and the resolution, *R,* between ondansetron related compound C and ondansetron related compound D is not less than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency determined from the analyte peak is not less than 400 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of ondansetron related compound D in the portion of Ondansetron Hydrochloride taken by the formula:

$$10(C/W)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Ondansetron Related Compound D RS in the *Standard solution; W* is the weight, in mg, of Ondansetron Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak ~~responses~~

■areas■2S (*USP27*)
obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.10% is found.

Change to read:

Chromatographic purity—

METHOD I—

Resolution solution—Dissolve ~~an accurately weighed quantity of USP Ondansetron Related Compound A RS~~

■a quantity of USP Ondansetron Resolution Mixture RS ■2S (*USP27*)
in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of ~~100 µg per mL.~~

■12.5 mg per mL.■2S (*USP27*)

~~*Identification solution*—Dissolve an accurately weighed quantity of USP Ondansetron Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of 100 µg per mL.~~

■■2S (*USP27*)
Standard solutions—Dissolve an accurately weighed quantity of USP Ondansetron Hydrochloride RS in methanol, and mix to obtain a solution having a known concentration of about 0.25 mg per mL. Dilute this solution quantitatively with methanol to obtain *Standard solutions,* designated below by letter, having the following compositions:

Standard solution	Dilution	Concentration (µg RS per mL)	Percentage (%, for comparison with test specimen)
A	(1 in 5)	50	0.4
B	(1 in 10)	25	0.2
C	(1 in 20)	12.5	0.1

Test solution—Dissolve an accurately weighed quantity of Ondansetron Hydrochloride in methanol to obtain a solution containing 12.5 mg per mL.

Procedure—Separately apply 20 µL of the *Test solution,* 20 µL of each *Standard solution,* and ~~10 µL of the *Identification solution*~~

■20 µL of the *Resolution solution*■2S (*USP27*)
to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. ~~To the same plate apply 20 µL of the *Test solution* and on top of this application apply 10 µL of the *Resolution solution* and 10 µL of the *Identification solution* to make a system suitability spot.~~

■■2S (*USP27*)
Develop the chromatogram in a solvent system consisting of a mixture of chloroform, ethyl acetate, methanol, and ammonium hydroxide (90:50:40:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. ~~Examine the plate under short wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the *Test solution* with those of the principal spots in the chromatograms of the *Standard solutions:* complete resolution of the three components of the system suitability spot, any secondary spot from the chromatogram of the *Test solution* having an R_F value corresponding to that of the principal spot of the *Identification solution* is not larger or more intense than the principal spot obtained from the *Standard solution A* (0.4%), and no other secondary spot from the chromatogram of the *Test solution*~~

~~having an R_F value corresponding to that of the principal spot of the *Resolution solution* is larger or more intense than the principal spot obtained from *Standard solution B* (0.2%), and the sum of the intensities of the secondary spots obtained from the *Test solution* corresponds to not more than 1.0%.~~

In-Process Revision

■Examine the plate under short-wavelength UV light: complete resolution of the three components of the *Resolution solution* spot is found. Compare the intensities of any secondary spots observed in the chromatogram of the *Test solution* with those of the principal spots in the chromatograms of the *Standard solutions:* any secondary spot from the chromatogram of the *Test solution* having an R_F value corresponding to that of the uppermost secondary spot of the *Resolution solution* is not larger or more intense than the principal spot obtained from *Standard solution A* (0.4%); and no other secondary spot from the chromatogram of the *Test solution* is larger or more intense than the principal spot obtained from *Standard solution B* (0.2%).■2S (*USP27*)

METHOD II—

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

Standard solution—Proceed as directed for the *Standard preparation* in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure— ~~Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Ondansetron Hydrochloride taken by the formula:~~

~~$100(r_i / r_u)$,~~

~~in which r_i is the peak response for each impurity, and r_u is the sum of the responses of all of the peaks: not more than 0.2% of any individual impurity is found, and the total of all impurities found is not more than 0.5%.~~

■Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Ondansetron Hydrochloride taken by the formula:

$$50{,}000(C/W)(1/F)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Ondansetron Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Ondansetron Hydrochloride taken to prepare the *Test solution; F* is the relative response factor of the impurities as described in the accompanying table; r_i is the peak area for each impurity in the *Test solution;* and r_S is the peak area of ondansetron obtained from the *Standard solution:* meets the requirements given in the accompanying table.

Compound name	Relative retention time	Relative response factor	Limit (%)
Ondansetron related compound C	about 0.32	1.2	0.2
Ondansetron related compound D*	about 0.34	1.3	0.1
Imidazole	about 0.49	0.3	0.2
2-methylimidazole	about 0.54	0.4	0.2
Ondansetron	1.0	—	—
Ondansetron related compound A	about 1.10	0.8	0.2
Unknown	—	1.0	0.1
Total	—	—	0.5

* Quantified in the test for *Limit of ondansetron related compound D.*■2S (*USP27*)

In-Process Revision

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of 0.02 M monobasic ~~potassium~~

■sodium■2S (*USP27*)
phosphate (previously adjusted with 1 M sodium hydroxide to a pH of 5.4) and acetonitrile (50:50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Ondansetron Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 90 µg per mL.

System suitability solution—Dissolve suitable quantities of USP Ondansetron Hydrochloride RS and USP Ondansetron Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 90 µg per mL and ~~50 µg~~

■20 µg■2S (*USP27*)
per mL, respectively.

Assay preparation—Transfer about 45 mg of Ondansetron Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 216-nm detector and a 4.6-mm × 20-cm column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for ondansetron and 1.1 for ondansetron related compound A; and the resolution, *R,* between ondansetron related compound A and ondansetron is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{18}H_{19}N_3O \cdot HCl$ in the portion of Ondansetron Hydrochloride taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Ondansetron Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak ~~responses~~

■areas■2S (*USP27*)
obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Papaverine Hydrochloride, *USP 26* page 1395—See briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-28

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Papaverine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

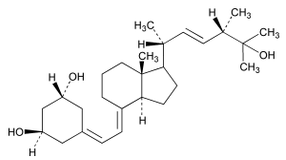
BRIEFING

Paricalcitol, page 647 of *PF* 29(3) [May–June 2003]. It is proposed to correct the absorbance ratio under *Identification* test *B*. Also, to avoid the problem of solubility and to conserve the USP Paricalcitol RS, it is proposed to prepare the *Standard solution* in the test for *Chromatographic purity* using USP Paricalcitol Solution RS.

(PA4: E. Gonikberg) RTS—40207-1

Add the following:

■Paricalcitol



$C_{27}H_{44}O_3$ 416.64

19-Nor-1-α,25-dihydroxyvitamin D_2

(1α,3β,7*E*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1,3,25-triol.

(7*E*,22*E*)-19-Nor-9,10-secoergosta-5,7,22-triene-1α,3β,25-triol [*131918-61-1*].

» Paricalcitol contains not less than 97.0 percent and not more than 103.0 percent of $C_{27}H_{44}O_3$, calculated on the dried basis.

Caution—Handle Paricalcitol with exceptional care because it is very potent. Care should be taken to prevent inhaling particles of Paricalcitol and exposing the skin to it.

Packaging and storage—Preserve in tight, light-resistant containers, and store under argon in a freezer.

USP Reference standards ⟨11⟩—*USP Paricalcitol RS. USP Paricalcitol Solution RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 5 µg per mL.

Medium: dehydrated alcohol.

Ratios: A_{243}/A_{251}, between 0.80 and 0.86; and ~~A_{251}/A_{261};~~ A_{261}/A_{251}, between 0.63 and 0.69.

Loss on drying (see *Thermal Analysis* ⟨891⟩)—Determine the percentage of volatile substances by thermogravimetric analysis on an appropriately calibrated instrument, using about 8 mg of Paricalcitol, accurately weighed. Heat at a rate of 5° per minute between ambient temperature and 150° in an atmosphere of nitrogen at a flow rate of 40 mL per minute. From the thermogram determine the accumulated loss in weight: it loses not more than 2.0% of its weight.

Chromatographic purity—

Diluent—Prepare a mixture of water and dehydrated alcohol (1:1).

Butylparaben solution—Transfer about 25 mg of butylparaben to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix

Solution A—Use filtered and degassed water.

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—~~Prepare a solution of USP Paricalcitol RS~~ Dilute USP Paricalcitol Solution RS in *Diluent* ~~having~~ to a known concentration of about 0.1 µg of paricalcitol per mL.

Control standard solution—Transfer 3.0 mL of the *Standard solution* to a 10.0-mL volumetric flask, dilute with *Diluent* to volume, and mix.

In-Process Revision

Test stock solution—Transfer about 10 mg of Paricalcitol, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with dehydrated alcohol to volume, and mix.

Resolution solution—Transfer 1 mL of the *Butylparaben solution* and 1 mL of the *Test stock solution* to a 100-mL volumetric flask, dilute with *Diluent* to volume, and mix. Transfer 1 mL of this solution to a 10-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Test solution—Prepare a mixture of the *Test stock solution* and water (1:1).

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 252-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 2 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–10	95	5	isocratic
10–30	95→45	5→55	linear gradient
30–40	45	55	isocratic
40–45	45→0	55→100	linear gradient
45–50	0	100	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between paricalcitol and butylparaben is not less than 12.0. Chromatograph the *Standard solution* and the *Control standard solution,* and record the peak responses as directed for *Procedure:* the area ratio for the paricalcitol peak from the *Standard solution* to that from the *Control standard solution* is between 1.8 and 4.0; and the relative standard deviation for replicate injections of the *Standard solution* is not more than 10.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Diluent, Standard solution,* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses, disregarding any peaks corresponding to those obtained from the *Diluent.* Calculate the percentage of each impurity in the portion of Paricalcitol taken by the formula:

$$10(C/W)(r_i / r_S),$$

in which C is the concentration, in µg per mL, of USP Paricalcitol RS in the *Standard solution; W* is the weight, in mg, of Paricalcitol taken to prepare the *Test stock solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the paricalcitol peak response obtained from the *Standard solution:* not more than 0.1% of any individual impurity is found; and not more than 0.5% of total impurities is found.

Assay—

Mobile phase—Prepare a filtered and degassed mixture of methanol and water (4:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a mixture of methanol and water (1:1).

Standard preparation—Prepare a solution of USP Paricalcitol RS in dehydrated alcohol having a known concentration of about 0.5 mg per mL. Dilute this solution quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 5.0 µg per mL.

Assay preparation—Transfer about 25 mg of Paricalcitol, accurately weighed, to a 50-mL low actinic volumetric flask, dissolve in and dilute with dehydrated alcohol to volume, and mix. Transfer 2.0 mL of this solution to a 200-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 252-nm detector and a 4.6-mm × 25-cm column that contains 5-µm

packing L1. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{27}H_{44}O_3$ in the portion of Paricalcitol taken by the formula:

$$5C(r_U / r_S),$$

in which C is the concentration, in µg per mL, of USP Paricalcitol RS in the *Standard preparation;* and r_U and r_S are the paricalcitol peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP27*)

BRIEFING

Paricalcitol Injection, page 649 of *PF* 29(3) [May–June 2003]. It is proposed to add a resolution requirement in the test for *Related compounds* to assure that the system is suitable to quantitate related compound D. It is also proposed to correct the concentrations of the *Standard solutions* under the *Limit of aluminum* test.

(PA4: E. Gonikberg) RTS—40207-2

Add the following:

■Paricalcitol Injection

» Paricalcitol Injection is a sterile solution of Paricalcitol in a mixture of Water for Injection, Propylene Glycol, and Alcohol. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of paricalcitol ($C_{27}H_{44}O_3$). It contains no antimicrobial agents.

Packaging and storage—Preserve in single-dose containers, preferably of Type I glass. Store at controlled room temperature.

USP Reference standards ⟨11⟩— *USP Endotoxin RS. USP Paricalcitol Solution RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Bacterial endotoxins ⟨85⟩—It contains not more than 10 USP Endotoxin Units per µg of paricalcitol.

Particulate matter ⟨788⟩: meets the requirements for small-volume injections.

Limit of aluminum ⟨206⟩—

Nitric acid diluent—Dilute 4 mL of nitric acid to 2000 mL with water.

Matrix modifier solution—Dissolve 1.5 g of magnesium nitrate in 1000 mL of water.

Standard stock solution—Proceed as directed in the chapter under *Standard Preparations,* beginning with "Treat some aluminum wire" and ending with "Cool, and transfer the solution, with the aid of water, to a 100-mL volumetric flask, dilute with water to volume, and mix." Transfer 2 mL of this solution to a second 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 2 mL of this solution to a third 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains about 0.4 µg of aluminum per mL.

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Standard solutions—Dilute accurately measured portions of the *Standard stock solution* with *Nitric acid diluent* to obtain solutions having known concentrations of about 2.5, 5.0, 10, 20, and 50 ~~µg~~ ng of aluminum per mL.

Test solution—Dilute 4.0 mL of Injection with 6.0 mL of *Nitric acid diluent* or use an appropriate dilution to obtain a solution having a concentration not greater than 0.02 µg of aluminum per mL.

System suitability solution—Dilute 9.5 mL of the *Test solution* with 0.5 mL of the *Standard stock solution.* If the resulting solution contains more than 0.04 µg of aluminum per mL, prepare an alternate dilution having a concentration between about 0.02 and 0.04 µg of aluminum per mL.

Procedure—Concomitantly determine the absorbances of the *Standard solutions, System suitability solution,* and *Test solution* at the aluminum emission line at 309.3 nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with an aluminum hollow-cathode lamp and a flameless electrically heated furnace. Under typical conditions, the sample volume is 20 µL, the volume of the *Matrix modifier solution* is 5 µL, the injection temperature is 100°, and the oven conditions are as follows [NOTE—These conditions may be optimized for each instrument]:

Step	Temperature
Drying 1	110°
Drying 2	130°
Drying 3	200°
Pyrrolysis	1100°
Read	2300°
Clean Out	2450°

Plot the absorbances of the *Standard solutions* versus the content of aluminum, in ng per mL, drawing a straight line best fitting the five points: the correlation coefficient is not less than 0.995; the recovery for the *System suitability solution* is between 80% and 120%; and the duplicate injections must agree within 0.0024 µg per mL. From the graph so obtained, determine the quantity of aluminum, *C,* in µg, found in each mL of the *Test solution.* Calculate the quantity, in µg, of aluminum in each mL of the Injection taken by the formula:

$$CD,$$

in which C is as defined above; and D is the dilution factor used to prepare the *Test solution:* not more than 0.5 µg per mL is found.

Related compounds—

Diluent—Prepare a mixture of water and acetonitrile (1:1).

Solution A—Prepare a filtered and degassed mixture of water and acetonitrile (85:15).

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Prepare a solution of USP Paricalcitol Solution RS in *Diluent* having a known concentration of paricalcitol equal to about 0.5% of the labeled concentration of the Injection.

Control standard solution—Transfer 5.0 mL of the *Standard solution* to a 25.0-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Degradation stock solution—Accurately dilute about 1 mL of USP Paricalcitol Solution RS with *Diluent* to 5 mL.

Degradation solution 1—Transfer about 1 mL of the *Degradation stock solution* and 0.1 mL of 30 percent hydrogen peroxide into a 10-mL container, and let stand at room temperature for 1 hour. Dilute with *Diluent* to 10 mL, and mix.

Degradation solution 2—Place about 1 mL of the *Degradation stock solution* and 1 mL of 0.1 N hydrochloric acid in a 10-mL container. Mix, and heat at 70° for 1 hour. Cool to room temperature, dilute with *Diluent* to 10 mL, and mix.

Test solution—Use the Injection.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 252-nm detector, a 4.6-mm × 7.5-cm guard column that contains packing L1, and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–25	65→5	35→95	linear gradient
25–45	5	95	isocratic

Chromatograph the *Standard solution* and the *Control standard solution,* and record the peak responses as directed for *Procedure:* the area ratio for the paricalcitol peak from the *Standard solution* to that from the *Control standard solution* is between 4.0 and 6.0; and the relative standard deviation for replicate injections of the *Standard solution* is not more than 5.0%.

Procedure—Chromatograph the *Degradation solution 1,* and identify the paricalcitol peak and the peaks due to the related compounds listed in *Table 1*.

Table 1.

Relative Retention Time	Name	Limit in the *Test solution,* (%)
0.63	Related compound A	1.0
0.79	Related compound B	1.0

Chromatograph the *Degradation solution 2,* and identify the paricalcitol peak and the peaks due to the related compounds listed in *Table 2*. The resolution, *R,* between the paricalcitol peak and the related compound D peak is not less than 1.0.

Table 2.

Relative Retention Time	Name	Limit in the *Test solution,* (%)
0.89	Related compound C	1.0
0.95	Related compound D	1.0
1.32	Related compound E*	1.0
1.57	Related compound F	1.0
1.66	Related compound G	1.0
1.74	Related compound H	1.0
1.79	Related compound I	1.0

* NOTE—This peak is very small (approximately 3 to 5 times the signal-to-noise ratio).

Separately inject equal volumes (about 100 to 200 µL) of the *Diluent* and the *Test solution,* in duplicate, into the chromatograph, record the chromatograms, and measure the peak responses, disregarding any peaks corresponding to those obtained from the *Diluent.* Calculate the percentage of each impurity in the portion of Injection taken by the formula:

$$100(C/L)(r_i/r_S),$$

in which C is the concentration, in µg per mL, of paricalcitol in the *Standard solution,* calculated on the basis of the content of paricalcitol in the USP Paricalcitol Solution RS; L is the labeled amount, in µg per mL, of paricalcitol in the Injection; r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the paricalcitol peak re-

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sponse obtained from the *Standard solution:* in addition to not exceeding the limits for impurities in *Tables 1* and *2,* not more than 2.0% of total impurities is found.

Content of propylene glycol and alcohol—

Mobile phase—Prepare a filtered and degassed 0.01 N sulfuric acid solution.

Alcohol standard solution—Transfer 2.0 mL of dehydrated alcohol to a 10-mL volumetric flask, dilute with water to volume, and mix.

Propylene glycol standard solution—Transfer 3.0 mL of propylene glycol to a 10-mL volumetric flask, dilute with water to volume, and mix.

Standard solution—Transfer 5.0 mL each of *Alcohol standard solution* and *Propylene glycol standard solution* to a 50-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer 5.0 mL of the Injection to a 50-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 7.8-mm × 30-cm column that contains packing L17. The column temperature is maintained at 60°. The flow rate is about 0.8 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the elution order is propylene glycol followed by alcohol; the resolution, *R,* between propylene glycol and the alcohol is not less than 4.0; and the relative standard deviation for replicate injections is not more than 2.0% for each peak.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatographs, and measure the responses for the major peaks. Calculate the percentage of propylene glycol and alcohol in the portion of Injection taken by the formula:

$$C(r_U / r_S),$$

in which C is the concentration, in percentage, of alcohol or propylene glycol in the *Alcohol standard solution* or *Propylene glycol standard solution,* respectively; and r_U and r_S are the corresponding peak responses obtained from the *Test solution* and *Standard solution,* respectively: between 16% and 24% of dehydrated alcohol is found; and between 26% and 34% of propylene glycol is found.

Other requirements—It meets the requirements under *Injections* ⟨1⟩.

Assay—

Diluent, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay* under *Paricalcitol.*

Standard preparation—Prepare a solution of USP Paricalcitol Solution RS in *Diluent* having a known concentration of paricalcitol similar to that of the Injection.

Assay preparation—Use the Injection.

Procedure—Separately inject equal volumes (about 100 to 200 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in µg, of paricalcitol ($C_{27}H_{44}O_3$) in each mL of the Injection taken by the formula:

$$C(r_U / r_S),$$

in which C is the concentration, in µg per mL, of paricalcitol in the *Standard preparation,* calculated on the basis of the content of paricalcitol in the USP Paricalcitol Solution RS; and r_U and r_S are the paricalcitol peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

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BRIEFING

Pentobarbital Sodium, *USP 26* page 1431 and page 657 of *PF* 29(3) [May–June 2003]. Because of the reported hygroscopic nature of this compound, it is proposed to indicate that the *Test solution* in the test for *Related compounds* and the *Standard preparation* in the *Assay* should be prepared at the same time as the test for *Loss on drying*. Molecular weights have been changed to reflect current atomic weight values published in *USP 26*.

(PA3: S. Salado) RTS—39792-1

Change to read:

» Pentobarbital Sodium contains not less than ~~98.5~~

■98.0■1S (*USP27*)
percent and not more than ~~101.0~~

■102.0■1S (*USP27*)
percent of $C_{11}H_{17}N_2NaO_3$, calculated on the dried basis.

Change to read:

Identification—

A: ~~The UV absorption spectrum of the *Assay preparation* corresponds to that of the *Standard preparation*, as obtained in the *Assay.*~~

■*Ultraviolet Absorption* ⟨197U⟩—

Solution: 10 µg per mL.

Medium: dilute ammonium hydroxide (1 in 200).■1S (*USP27*)

B:

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

C: ■1S (*USP27*)
Ignite about 200 mg: the residue effervesces with acids, and meets the requirements of the tests for *Sodium* ⟨191⟩.

Add the following:

■**Related compounds—**

Mobile phase—Prepare as described in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Pentobarbital RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.001 mg per mL.

Test solution—Transfer about 110 mg of Pentobarbital Sodium, accurately weighed, to a 100-mL volumetric flask, add about 80 mL of *Mobile phase,* and sonicate until dissolved. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 2.5; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 15.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Pentobarbital Sodium taken by the formula:

$$(248.25/226.27)(10{,}000/F)(C/W)(r_i/r_S),$$

in which 248.25 and 226.27 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; C is the concentration, in mg per mL, of USP Pentobarbital RS in the *Standard solution; F* is the relative response factor of the impurity according to the table below; W is the weight, in mg, of Pentobarbital Sodium, on the dried basis, used to prepare the *Test solution;* r_i is the peak area for any impurity

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in the *Test solution;* and r_S is the peak area for Pentobarbital in the *Standard solution:* the impurities meet the requirements given in the table below:

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
6-Imino-5-ethyl-5-(1-methylbutyl)barbituric acid	about 0.39	1.5	0.2
Pentobarbital	1.0	—	—
5-Ethyl-5-(1,3-dimethylbutyl) barbituric acid	about 1.5	0.9	0.3
Unknown impurities	—	1.0	0.1
Total	—	—	0.5

■1S (*USP27*)

Change to read:

Assay—

~~*Diluting solvent*—Use freshly prepared dilute ammonium hydroxide (1 in 200).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Pentobarbital RS in *Diluting solvent* to obtain a solution having a known concentration of about 10 µg per mL.~~

~~*Assay preparation*—Transfer about 25 mg of pentobarbital sodium, previously dried and accurately weighed, in a 50-mL volumetric flask, immediately dilute with *Diluting solvent* to volume, and mix. Pipet 2 mL of this solution into a 100-mL volumetric flask, add *Diluting solvent* to volume, and mix.~~

~~*Procedure*—Concomitantly determine the absorbances of the *Assay preparation* and the *Standard preparation* in 1-cm cells at the wavelength of maximum absorbance at about 240 nm, with a suitable spectrophotometer, using *Diluting solvent* as the blank. Calculate the quantity, in mg, of $C_{11}H_{17}N_2NaO_3$ in the portion of Pentobarbital Sodium taken by the formula:~~

~~$$2.5C(248.26/226.28)(A_U/A_S),$$~~

~~in which *C* is the concentration, in µg per mL, of USP Pentobarbital RS in the *Standard preparation;* 248.26 and 226.28 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.~~

■NOTE—Use the value for *Loss on drying* obtained at the same time as the preparation of the *Test solution* in the test for *Related compounds* and the *Assay preparation* in the *Assay.*■2S (*USP27*)

■*Mobile phase, Standard preparation,* and *Chromatographic system*—Proceed as described in the *Assay* under *Pentobarbital.*

Assay preparation—Transfer about 110 mg of Pentobarbital Sodium, accurately weighed, to a 100-mL volumetric flask, add about 80 mL of *Mobile phase,* and sonicate until dissolved. Dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the major peak. Calculate the quantity, in mg, of $C_{11}H_{17}N_2NaO_3$ in the portion of Pentobarbital Sodium taken by the formula:

$$(248.25/226.27)1000C(r_U/r_S),$$

in which 248.25 and 226.27 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; *C* is the concentration, in mg per mL, of USP Pentobarbital RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP27*)

BRIEFING

Camphorated Phenol Topical Gel. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The *Assay* is based on analysis performed with a 2-mm × 1.8-m glass column with 100- to 120-mesh S1A packing, coated with 15% G44.

(PA7b: B. Davani) RTS—40196-1

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Add the following:

■Camphorated Phenol Topical Gel

» Camphorated Phenol Topical Gel is a mixture of camphor and phenol in a suitable gel vehicle. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of camphor ($C_{10}H_{16}O$) and phenol (C_6H_6O).

Packaging and storage—Preserve in tight containers. Store at room temperature, avoid excessive heat and close cover after each use.

USP Reference standards ⟨11⟩—*USP Camphor RS. USP Phenol RS.*

Identification—The retention times of the camphor and phenol peaks in the chromatograms of the *Assay preparation* correspond to those of the *Standard preparation* obtained as directed in the *Assay* for camphor and phenol.

Assay—

Internal standard solution—Transfer 250 mg, accurately weighed, of *n*-dodecane to a 25-mL volumetric flask, dilute with chloroform to volume, and mix.

Standard preparation—Transfer about 96 mg of USP Phenol RS, accurately weighed, to a 10-mL volumetric flask. Add about 224 mg of USP Camphor RS, accurately weighed, to the flask. Dilute with chloroform to volume, and mix. Combine 5.0 mL of this solution with 5.0 mL of *Internal standard solution* in a 50-mL volumetric flask, dilute with chloroform to volume, and mix.

Assay preparation—Transfer about 1 g of Topical Gel, accurately weighed, to a 50-mL flask. Add 5.0 mL of *Internal standard solution,* dilute with chloroform to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector (200°) and a 2-mm × 1.8-m glass column packed with 100- to 120-mesh S1A, coated with 15% G44. The carrier gas is helium. Adjust the column temperature to about 140° so that the relative retention times are 0.3 for phenol, 0.8 for camphor, and 1.0 for the internal standard. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the camphor peak and the internal standard peak is not less than 2.0 and between the phenol peak and the camphor peak is not less than 5.0; and the relative standard deviation of the peak response ratio of the camphor peak and phenol peak to the internal standard peak for five consecutive injections of the *Standard preparation* is not more than 2.0%.

Procedure—Inject 1 to 2 µL of the *Assay preparation* and the *Standard preparation* into the gas chromatograph, record the chromatograms, and determine the peak response ratios. Calculate the percentage of camphor (*w*/*w*) and the percentage of phenol (*w*/*w*) in the sample according to the formula:

$$(50W_R / W)(r_U / r_S),$$

in which W_R is the weight, in mg, of the appropriate USP Reference Standard in the *Standard preparation; W* is the weight of Topical Gel, in mg, taken to prepare the *Assay preparation;* and r_U and r_S are the response ratios of the corresponding analyte peaks in the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

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BRIEFING

Camphorated Phenol Topical Solution. Because there is no existing *USP* monograph for this drug product, a new monograph is being proposed. The *Assay* is based on analysis performed with a 2-mm × 1.8-m glass column with 100- to 120-mesh S1A packing, coated with 15% G44.

(PA7b: B. Davani) RTS—40081-1

Add the following:

■Camphorated Phenol Topical Solution

» Camphorated Phenol Topical Solution is a solution of camphor and phenol in Eucalyptus Oil and Light Mineral Oil. It contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of camphor ($C_{10}H_{16}O$) and phenol (C_6H_6O).

Packaging and storage—Preserve in tight containers. Store at room temperature, avoid excessive heat, and close cover after each use.

USP Reference standards ⟨11⟩—*USP Camphor RS. USP Phenol RS.*

Identification—The retention times of the camphor and phenol peaks in the chromatograms of the *Assay preparation* correspond to those of the *Standard preparation*, obtained as directed in the *Assay.*

Specific gravity ⟨841⟩: between 0.861 and 0.865.

Assay—

Internal standard solution—Transfer 250 mg, accurately weighed, of *n*-dodecane to a 25-mL volumetric flask, dilute with chloroform to volume, and mix.

Standard preparation—Transfer about 96 mg of USP Phenol RS, accurately weighed, to a 10-mL volumetric flask. Add about 224 mg of USP Camphor RS, accurately weighed, to the flask. Dilute with chloroform to volume, and mix. Combine 5.0 mL of this solution with 5.0 mL of *Internal standard solution* in a 50-mL volumetric flask, dilute with chloroform to volume, and mix.

Assay preparation—Transfer about 1 g of Topical Solution, accurately weighed, to a 50-mL volumetric flask. Add 5.0 mL of *Internal standard solution,* dilute with chloroform to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector (200°) and a 2-mm × 1.8-m glass column packed with 100- to 120-mesh S1A, coated with 15% G44. The carrier gas is helium. Adjust the column temperature to about 140° so that the relative retention times are 0.3 for phenol, 0.8 for camphor, and 1.0 for the internal standard. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the camphor peak and the internal standard peak is not less than 2.0 and between the phenol peak and the camphor peak not less than 5.0; and the relative standard deviation of the peak response ratio of the camphor peak and the phenol peak to the internal standard peak for five consecutive injections of the *Standard preparation* is not more than 2.0%.

Procedure—Separately inject 1 to 2 µL of the *Assay preparation* and the *Standard preparation* into the gas chromatograph, record the chromatograms, and determine the peak response ratios. Calculate the percentage of camphor (*w*/*w*) and the percentage of phenol (*w*/*w*) in the portion of Topical Solution taken by the formula:

$$(50W_R/W)(R_U/R_S),$$

in which W_R is the weight, in mg, of the appropriate USP Reference Standard in the *Standard preparation; W* is the weight of Topical Solution, in mg, taken to prepare the *As-*

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say preparation; and R_U and R_S are the response ratios of the corresponding analyte peaks in the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Phentolamine Mesylate, *USP 26* page 1455—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-29

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Phentolamine Mesylate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Phenylbutazone Tablets, *USP 26* page 1458. It is proposed to change the pH of the *Medium* in the test for *Dissolution* from 6.8 to 7.5 to better reflect the test conditions as submitted in a supplement to FDA. In addition, editorial style changes have been made.

(BPC: M. Marques) RTS—36042-1

Change to read:

Dissolution ⟨711⟩—
Medium:

■pH 7.5■2S (*USP27*)
simulated intestinal fluid TS (without the enzyme); 900 mL.
Apparatus 1: 100 rpm.
Time: 30 minutes.
Procedure—Determine the amount of $C_{19}H_{20}N_2O_2$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 264 nm on filtered portions of the solution under test, suitably diluted, if necessary, with *Dissolution Medium,* using a suitable spectrophotometer, 1-cm cells, and *Dissolution Medium* as the blank, in comparison with a solution of known concentration of USP Phenylbutazone RS in the same *Medium*.
Tolerances—Not less than 70% *(Q)* is dissolved in 30 minutes.

BRIEFING

Potassium Chloride, *USP 26* page 1502 and page 1064 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-21

Change to read:

Packaging and storage—Preserve in well-closed containers.~~and store at up to 25 ± 2°.~~

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Where Potassium Chloride is intended for use in hemodialysis, it is so labeled.

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

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Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Change to read:

Iodide or bromide~~— Dissolve 2 g in 6 mL of water, add 1 mL of chloroform, and then add, dropwise, with constant agitation, 5 mL of a mixture of equal parts of chlorine TS and water: the chloroform is free from even a transient violet or a permanent orange color.~~

■IODIDE—

Standard stock solution—Transfer an accurately weighed quantity, about 41 mg, of potassium iodide to a 25-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Standard solution—Dilute 1.0 mL of *Standard stock solution* with water to 25 mL, and mix. Dilute 2.0 mL of this solution with water to 8 mL, and proceed as directed for *Test solution* beginning with "Add 1 mL each of chloroform".

Test solution—Dissolve 2 g of Potassium Chloride in 8 mL of water. Add 1 mL each of chloroform and diluted hydrochloric acid, then add 2 drops of a chloramine T solution (0.1 in 100), and shake gently. The violet color of the chloroform layer is not darker than that of a concomitantly prepared *Standard solution:* the limit is 0.005%.

BROMIDE—

Standard solution—Transfer an accurately weighed quantity, about 32 mg, of sodium bromide to a 25-mL volumetric flask. Dissolve in and dilute with water to volume, and mix. Dilute 2.0 mL of this solution with water to 8 mL, and proceed as directed for *Test solution* beginning with "Add 1 mL each of chloroform".

Test solution—Dissolve 2 g of Potassium Chloride in 8 mL of water. Add 1 mL each of chloroform and diluted hydrochloric acid, then add 5 drops of a chloramine T solution (1 in 100), and shake gently. The brown color of the chloroform layer is not darker than that of a concomitantly prepared *Standard solution:* the limit is 0.1%.■2S (*USP27*)

Add the following:

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

BRIEFING

Dibasic Potassium Phosphate, *USP 26* page 1517—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-17

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Dibasic Potassium Phosphate is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Potassium Phosphates Injection*. Where the label states that Dibasic Potas-

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sium Phosphate must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Potassium Phosphates Injection*.■2S (*USP27*)

BRIEFING

Povidone-Iodine, *USP 26* page 1520. It is proposed to revise the acceptance criterion in the test for *Residue on ignition* to define the quantity in numerical terms. The value (0.50 mg from 2 g) is consistent with the definition of "negligible" found in the USP *General Notices and Requirements*.

(PA7b: B. Davani) RTS—38899-1

Change to read:

Residue on ignition ⟨281⟩: ~~negligible,~~

■not more than 0.025%,■2S (*USP27*)
from 2 g.

BRIEFING

Pralidoxime Chloride, *USP 26* page 1521—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-18

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Prednisolone Acetate, *USP 26* page 1529—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-17

Change to read:

Packaging and storage—Preserve in well-closed containers.
■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Prednisolone Acetate is sterile, it meets the requirements for *Sterility* under *Prednisolone Acetate Injectable Suspension*.■2S (*USP27*)

BRIEFING

Prilocaine Hydrochloride, *USP 26* page 1536—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-22

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

In-Process Revision

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Prilocaine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Procainamide Hydrochloride, *USP 26* page 1543—See briefing under *Amifostine.*

(PA5: A. Wilk) RTS—40124-30

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Procainamide Hydrochloride RS. USP Aminobenzoic Acid RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Procaine Hydrochloride, *USP 26* page 1547—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-23

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Prochlorperazine Edisylate, *USP 26* page 1551—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-19

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Prochlorperazine Maleate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Progesterone, *USP 26* page 1554—See briefing under *Alprostadil.*

(PA1: C. Anthony) RTS—40156-18

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Progesterone is sterile, it meets the requirements for *Sterility* under *Progesterone Injectable Suspension.*■2S (*USP27*)

BRIEFING

Promazine Hydrochloride, *USP 26* page 1558—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-24

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Promazine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

In-Process Revision

Add the following:

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

BRIEFING

Promethazine Hydrochloride, *USP 26* page 1560—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-25

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Promethazine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Propoxycaine Hydrochloride, *USP 26* page 1566—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-26

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Propoxycaine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Propoxycaine Hydrochloride is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection*. Where the label states that Propoxycaine Hydrochloride must be subjected to further processing during the prepara-

tion of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Propoxycaine and Procaine Hydrochlorides and Levonordefrin Injection*.■2S (*USP27*)

BRIEFING

Propranolol Hydrochloride, *USP 26* page 1577 and page 2993 of the *First Supplement*—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-31

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Propranolol Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Quinidine Gluconate, *USP 26* page 1605—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-32

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Quinidine Gluconate RS. USP Quininone RS.

Add the following:

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

In-Process Revision

BRIEFING

Quinidine Gluconate Extended-Release Tablets, *USP 26* page 1606. Because FDA recently approved an ANDA for this drug product, it is proposed to add a new *Drug release Test 5*. The new product was approved with a *Drug release* test that differs from those currently official in the *USP* monograph because of differences in dissolution rates *in vitro*. In the absence of any adverse comment, it is proposed to implement this revision via the *First Interim Revision Announcement* pertaining to *USP 27–NF 22,* with an official date of February 1, 2004.

(BPC: M. Marques) RTS—38538-1

Change to read:

Drug release ⟨724⟩—

Test 1: If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 1*.

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

Apparatus 2: 75 rpm.

Times: 1 hour, 2 hours, 4 hours, 8 hours.

Procedure—Determine the amount of $C_{20}H_{24}N_2O_2 \cdot C_6H_{12}O_7$ dissolved from UV absorbances at the wavelength of maximum absorbance at about 235 nm, using filtered aliquots of the solution under test, diluted with *Dissolution Medium* if necessary, in comparison with a Standard solution having a known concentration of USP Quinidine Gluconate RS in the same medium.

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

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

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

Medium: 0.1 N hydrochloric acid; 600 mL.

Apparatus 2: 75 rpm.

Times and *Procedure*—Proceed as directed for *Test 1.*

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

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

•*Test 5:* If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 5*.

Medium, Apparatus, and *Procedure*—Proceed as directed for *Test 1,* using 8-mesh sinker baskets.*

Times: 1, 2, and 4 hours.

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

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

•1

BRIEFING

Ranitidine Hydrochloride, *USP 26* page 1615—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-20

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Ranitidine Hydrochloride RS. USP Ranitidine Related Compound A RS. USP Ranitidine Related Compound B RS. USP Ranitidine Related Compound C RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

* A suitable sinker is available from VanKel, www.varianinc.com, catalog number 12-3062.

In-Process Revision

Add the following:

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

BRIEFING

Reserpine, *USP 26* page 1625—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-33

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Reserpine RS*.

■*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Ritodrine Hydrochloride, *USP 26* page 1652—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-19

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Ritodrine Hydrochloride RS*.

■*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

■**Other requirements**—Where the label states that Ritodrine Hydrochloride is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Ritodrine Hydrochloride Injection*. Where the label states that Rito-

drine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Ritodrine Hydrochloride Injection*.■2S (*USP27*)

BRIEFING

Selenious Acid, *USP 26* page 1675—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-21

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

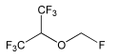
BRIEFING

Sevoflurane, page 2577 of *PF* 27(3) [May–June 2001]. The test for *Chromatographic purity* is being replaced with a test for *Related compounds* which is more precise and robust. The gas chromatographic procedure in this test is based on analyses performed with the Rt-1000 brand of G35 column.

(AER: K. Zaidi) RTS—39471-1

Add the following:

■Sevoflurane



$C_4H_3F_7O$ ~~200.06~~ 200.05

Propane, 1,1,1,3,3,3-hexafluoro-2-(fluoromethoxy)-.

Fluoromethyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether [*28523-86-6*].

» Sevoflurane contains not less than ~~99.9~~ 99.97 percent and not more than ~~100.0~~ 100.00 percent of $C_4H_3F_7O$, calculated on the anhydrous basis.

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

USP Reference standards ⟨11⟩—*USP Sevoflurane RS. USP Sevoflurane Related Compound A RS. USP Sevomethyl Ether (SME) RS. USP Hexafluoroisopropanol RS.*

Identification, *Infrared Absorption—*The IR absorption spectrum of Sevoflurane, obtained using a gas cell, exhibits maxima only at the same wavelengths as that of a similar preparation of USP Sevoflurane RS.

Refractive index ⟨831⟩: between 1.2745 and 1.2760, at 20°.

Acidity or alkalinity—Transfer 20.0 mL of Sevoflurane and 20.0 mL of carbon dioxide-free water to a separatory funnel, shake for 3 minutes, and allow the layers to separate: the aqueous layer requires not more than 0.10 mL of 0.010

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N sodium hydroxide or not more than 0.60 mL of 0.010 N hydrochloric acid for neutralization, bromocresol purple TS being used as the indicator.

Water, *Method I* ⟨921⟩: ~~between 0.03% and 0.2%.~~ not more than ~~0.2%;~~ 0.1%. ~~and, when packaged in glass containers, not less than 0.03%.~~

Limit of fluoride—[NOTE—Use plastic utensils throughout this test.]

Buffer solution—Transfer 110 g of sodium chloride and 1 g of sodium citrate to a 2000-mL volumetric flask, and dissolve in 700 mL of water. Carefully add 150 g of sodium hydroxide, and shake to dissolve. Cool to room temperature, and carefully add 450 mL of glacial acetic acid while stirring. Cool, add 600 mL of isopropyl alcohol, dilute with water to volume, and mix. [NOTE—The pH of this solution is between 5.0 and 5.5. This solution may be used for six weeks when stored at room temperature.]

Solution A—Transfer about 221 mg of sodium fluoride, previously dried at 150° for 4 hours and accurately weighed, to a 100-mL volumetric flask. Add about 20 mL of water, and mix to dissolve. Add 1.0 mL of 0.01 N sodium hydroxide, and dilute with water to volume. Each mL of this solution contains 1 mg of fluoride. Store in a tightly closed plastic container. [NOTE—This solution may be used for two weeks when stored in a refrigerator.]

Standard stock solutions—Quantitatively transfer accurately measured volumes of *Solution A* to separate 100-mL volumetric flasks, and dilute with water to obtain solutions having known concentrations of about 5, 2, 0.5, and 0.2 µg of fluoride per mL.

Standard solutions—Transfer 25.0 mL of each of the *Standard stock solutions* to separate 50-mL volumetric flasks, dilute with *Buffer solution* to volume, and mix.

Test solution—Pipet 50.0 mL of Sevoflurane and 50.0 mL of water into a separatory funnel, shake vigorously for 3 minutes, and allow the liquids to separate completely. Transfer 25.0 mL of the aqueous top layer to a 50-mL volumetric flask, dilute with *Buffer solution* to volume, and mix.

Procedure—Concomitantly measure the potentials, in mV, of the *Standard stock solutions, Standard solutions,* and *Test solution* with a pH meter (see *pH* ⟨791⟩) capable of a minimum reproducibility of ±0.2 mV and equipped with a fluoride-specific ion-indicating electrode and a glass-sleeved calomel reference electrode. [NOTE—When taking measurements, transfer the solution under test to a 100-mL beaker containing a polytef-coated stirring bar, and immerse the electrodes. Allow to stir on a magnetic stirrer having an insulated top until equilibrium is attained in about 2 to 3 minutes, and record the potential. Rinse the electrodes with the *Buffer solution,* and dry, taking care to avoid damaging the crystal of the specific-ion electrode. A satisfactory response is achieved if the difference between the potentials obtained with the *Standard stock solutions* having fluoride concentrations of 5 and 0.5 µg per mL is in the range between 50 and 60 mV.] Plot the logarithms of the fluoride concentrations, in µg per mL, of the *Standard solutions* versus potentials, in mV. From the graph so obtained and the measured potential of the *Test solution,* determine the concentration, in µg per mL, of fluoride in the *Test solution:* not more than 2 µg per mL is found.

Limit of nonvolatile residue—Transfer 10.0 mL of Sevoflurane to an accurately weighed evaporating dish, evaporate to dryness on a steam bath, and dry the residue at 105° for 2 hours: the weight of the residue does not exceed 1.0 mg.

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Limit of peroxide—

Titanium tetrachloride solution—Separately cool 1.0 mL of 6 N hydrochloric acid and 1.0 mL of titanium tetrachloride in small beakers surrounded by crushed ice. Add titanium tetrachloride dropwise to the chilled acid. Allow to stand at ice-bath temperature until all of the yellow solid dissolves, dilute with 6 N hydrochloric acid to 100 mL, and mix.

Standard stock solution—Prepare a solution of 30 percent hydrogen peroxide in water (1 in 400).

Standard solution—Transfer 15.0 mL of the *Standard stock solution* to a 1000-mL volumetric flask, dilute with water to volume, and mix. Transfer 1.0 mL of the solution so obtained and 5.0 mL of *Titanium tetrachloride solution* to a 10-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer 50.0 mL of Sevoflurane and 5.0 mL of *Titanium tetrachloride solution* to a separatory funnel, shake vigorously, allow the layers to separate, drain, and discard the lower layer. Carefully collect the top layer in a 10-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard solution* and the *Test solution* at a wavelength of about 410 nm, with a suitable spectrophotometer, using a 1-cm cell and a mixture of *Titanium tetrachloride solution* and water (1:1) as the blank. Calculate the peroxide concentration, in µg per mL, in the portion of Sevoflurane taken by the formula:

$$0.22(A_U / A_S),$$

in which A_U and A_S are the absorbances obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.22 µg per mL is found.

~~**Chromatographic purity—**~~

~~*Internal standard solution*—Use dimethoxymethane.~~

~~*Standard solutions*—Prepare two solutions, proceeding for each as follows. Transfer 2.0 mL of ethylene dichloride into a screw-capped vial, immediately seal with a cap and septum, and place on a balance. Using a microsyringe, transfer about 20 µL of USP Sevoflurane RS, accurately measured, to the vial by inserting the syringe needle through the septum. Record the quantity, in mg, of USP Sevoflurane RS added. Using the same method, transfer about 20 µL of *Internal standard solution* to the vial, and record the quantity, in mg, of the *Internal standard solution* added.~~

~~*Test solution*—Transfer 20.0 mL of Sevoflurane to a vial, and insert the stopper. Using a microsyringe, add 5 µL of *Internal standard solution*, accurately measured, to the vial.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.32-mm × 30-m fused-silica capillary column coated with a 3.0-µm film of liquid phase G19. Prior to use, condition the column overnight at a temperature of 250°. The column temperature is programmed as follows. Initially it is maintained at 40° for 10 minutes, then increased at a rate of 10° per minute to 200°, and maintained at 200° for at least 14 minutes. The injection port temperature is maintained at 200°. The detector temperature is maintained at 225°. The split ratio is 1:20. Helium is used as the carrier gas, flowing at a rate of about 1.0 mL per minute. Chromatograph one of the *Standard solutions,* and record the chromatograms as directed for *Procedure,* adjusting the recorder sensitivity to obtain the sevoflurane peak on scale: the relative retention times are 0.57 for 1,1,3,3-pentafluoroisopropenyl fluoromethyl ether, 0.62 for methyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether, 0.74 for sevoflurane, and 1.0 for the internal standard; the column efficiency is not less than 6000 theoretical plates; and the relative stan-~~

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dard deviation for replicate injections is not more than 2.0%. Chromatograph the *Test solution,* adjusting the recorder sensitivity to obtain peak heights of at least 10% of full scale for the two impurities, and record the chromatograms as directed for *Procedure:* the resolution, *R,* between these two impurities is not less than 2.0.

Procedure—Separately inject equal volumes (about 2 µL) of the *Standard solutions* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the major peaks. Calculate the relative response factor, *F,* for each of the *Standard solutions* by the formula:

$$(W_s/W_S)R_S,$$

in which W_s is the weight, in mg, of the internal standard in the *Standard solution;* W_S is the weight, in mg, of USP Sevoflurane RS in the *Standard solution;* and R_S is the average response ratio of the sevoflurane peak to that of the internal standard obtained from the *Standard solutions:* the relative response factors for the *Standard solutions* do not differ by more than 3.0% from their average. Calculate the quantity, in µg per g, of each impurity in the portion of Sevoflurane taken by the formula:

$$250(0.859/1.525)(R_u/F),$$

in which 0.859 and 1.525 are the specific gravities of the internal standard and sevoflurane, respectively; R_u is the response ratio of the impurity peak to that of the internal standard obtained from the *Test solution;* and *F* is the average relative response factor obtained as directed above: not more than 25 µg per g of 1,1,3,3-pentafluoroisopropenyl fluoromethyl ether, not more than 50 µg per g of methyl 2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether, and not more than 25 µg per g of any other individual impurity are found; and not more than 50 µg per g of total impurities, excluding the two named above, is found.

Internal standard solution—Use dimethoxymethane.

Standard solution 1—Transfer 2.0 mL of ethylene dichloride to a screw-capped vial, immediately seal with a cap and septum, and place on a balance. Inject about 20 µL of USP Sevoflurane RS and 20 µL of the *Internal standard solution,* both accurately measured, into the vial through the septum, and weigh the vial after each injection.

Standard solution 2—Transfer 2.0 mL of ethylene dichloride to a screw-capped vial, immediately seal with a cap and septum, and place on a balance. Inject about 20 µL of USP Sevoflurane Related Compound A RS and 20 µL of the *Internal standard solution,* both accurately measured, into the vial through the septum, and weigh the vial after each injection.

Test solution—Transfer 20.0 mL of Sevoflurane to a vial, and insert the stopper. Using a microsyringe, add about 5 µL of the *Internal standard solution,* accurately measured, to the vial.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and contains a 0.32-mm × 30-m fused-silica capillary column coated with a 3.0-µm film of liquid phase G43. Prior to use, condition the column overnight at a temperature of 250°. The carrier gas is helium, flowing at a rate of about 1.0 mL per minute. The chromatograph is programmed as follows. Initially the column temperature is maintained at 40° for 10 minutes, then it is increased at a rate of 10° per minute to 200°, and maintained at 200° for not less than 14 minutes. The injection port temperature is maintained at 200°, and the detector temperature is maintained at 225°. The split ratio is 1:20. Chromatograph *Standard solution 1* and *Standard solution 2,* and record the peak responses as directed for *Procedure,* adjusting the recorder sensitivity to obtain the sevoflurane peak on scale: the relative retention times are about 0.57 for sevoflurane related compound A, 0.74 for sevoflurane, and 1.0 for the internal

In-Process Revision

~~standard; the resolution, *R,* between sevoflurane and sevoflurane related compound A is not less than 2.0; the column efficiency is not less than 6000 theoretical plates; and the relative standard deviation for replicate injections, determined from the peak area ratio of sevoflurane to the internal standard, is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 2 µL) of *Standard solution 1, Standard solution 2,* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the major peaks. Calculate the relative response factor, *F,* for each *Standard solution* taken by the formula:~~

$$R_S(W_I/W_S),$$

~~in which R_S is the peak area ratio of sevoflurane to the internal standard obtained from the chromatogram; W_I is the weight, in mg, of the internal standard in the particular *Standard solution;* and W_S is the weight, in mg, of USP Sevoflurane RS or USP Sevoflurane Related Compound A RS in the corresponding *Standard solution.* Calculate the quantity, in µg per g, of sevoflurane related compound A in the portion of Sevoflurane taken by the formula:~~

$$250(R_U/F),$$

~~in which R_U is the peak response ratio of sevoflurane related compound A to the internal standard obtained from the *Test solution;* and *F* is the relative response factor obtained as directed above: not more than 25 µg per g of sevoflurane related compound A is found. Calculate the quantity, in µg per g, of each impurity, other than sevoflurane related compound A, in the portion of Sevoflurane taken by the formula:~~

$$250(R_U/F),$$

~~in which R_U is the peak response ratio of each impurity to the internal standard obtained from the *Test solution;* and *F* is the average relative response factor obtained as directed above: not more than 100 µg per g of any impurity, other than sevoflurane related compound A, is found; and not more than 300 µg per g of total impurities is found.~~

Related compounds—

Standard stock solution—Accurately weigh 10 mL (15 g) of USP Sevoflurane RS in a suitable vial fitted with a septum, and successively add 25 µL (~0.0375 g) each of USP Sevoflurane Related Compound A RS, USP Sevomethyl Ether (SME) RS, and USP Hexafluoroisopropanol RS. Record the weight after addition of each impurity.

Standard solution—Accurately weigh about 20 mL of USP Sevoflurane RS in a suitable vial fitted with a septum, and add 0.2 mL (~0.3 g) of the *Standard stock solution.* Record the exact weight of *Standard stock solution* added.

Test solution—The test sample is used as is.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and contains a 2.1-mm × 4-m silicosteel column packed with 5% G35 on 80- to 100-mesh support S12. The carrier gas is helium, flowing at a rate of 25 mL per minute. Initially the column temperature is maintained at 70° for 20 minutes, then it is increased at a rate of 8° per minute to 170°, and maintained at 170° for 17.5 minutes. The injection port temperature is maintained at 175°, and the detector temperature is maintained at 200°. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are 0.67 for sevoflurane related compound A, 1.0 for sevomethyl ether, and 2.88 for hexafluoroisopropanol; the resolution, *R,* between sevoflurane related compound A and sevomethyl ether is not less

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than 6; and the relative standard deviation, determined from the sevomethyl ether peak, for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 2 µL) of *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of all the peaks. Record the chromatogram for at least 50 minutes. Calculate the relative response factors, *F,* of sevoflurane related compound A and hexafluoroisopropanol relative to that of sevomethyl ether taken by the formula:

$$(C_S / C_{SME\text{-}std})(r_{SME\text{-}std} / r_S),$$

in which C_S and r_S are the concentration and the peak area for either sevoflurane related compound A or hexafluoroisopropanol in the *Standard solution* and $C_{SME\text{-}std}$ and $r_{SME\text{-}std}$ are the concentration and the peak area for sevomethyl ether in the *Standard solution.* The calculated relative response factors for sevoflurane related compound A and hexafluoroisopropanol must be in the range of 1.08 to 1.31 and 2.28 to 2.79, respectively.

Calculate the percentages (w/w) of impurities present in the *Test solution,* which are also found in the *Standard solution,* by the formula:

$$C_S(r_i / r_S),$$

in which r_i and r_S are the peak responses of impurities in the *Test solution* and in the *Standard solution;* and C_S is the concentration (*w/w*) of the impurities in the *Standard solution.* The other known impurities, that are not present in the *Standard solution,* are identified by their relative retention times and their amounts present are determined using their respective relative response factors (*Table 1*) by the formula:

$$FC_{SME\text{-}std}\,(r_i / r_{SME\text{-}std}).$$

Use relative response factor of SME to calculate the unknown impurities. *F* is the relative response factor of the known impurity not present in the *Standard solution;* $C_{SME\text{-}std}$ is the concentration (w/w) of SME in the *Standard solution;* and $r_{SME\text{-}std}$ is the peak area of SME in the *Standard solution.*

Table 1.

Impurity	Relative Retention Time	Relative Response Factor
Sevomethyl ether	1	1
2-Chloropropane	0.48	0.4092
Dichloromethane	0.76	1.5141
Chlorosevo ether	2.23	1.0884
Hexafluoroisopropyl formate	1.47	1.3068
Unknown impurities		1

Not more than 0.0025% of sevoflurane related compound A is found; not more than 0.01% of any other single impurity is found; and not more than 0.03% of total impurities is found.

Assay—Using the results from the test for *Related compounds,* calculate the percentage of $C_4H_3F_7O$ in the volume of Sevoflurane taken by subtracting the sum of percentages for all impurities found from ~~100.0%.~~ 100.00%.■2S (*USP27*)

BRIEFING

Sodium Acetate, *USP 26* page 1686—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-27

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Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate whether it is the trihydrate or is anhydrous. Where Sodium Acetate is intended for use in hemodialysis, it is so labeled.

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Sodium Bicarbonate, *USP 26* page 1687—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-22

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Where Sodium Bicarbonate is intended for use in hemodialysis, it is so labeled.

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Sodium Nitrite, *USP 26* page 1700—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-34

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

In-Process Revision

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Sodium Nitroprusside, *USP 26* page 1700—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-35

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Dibasic Sodium Phosphate, *USP 26* page 1702—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-23

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate whether it is dried or is the monohydrate, the dihydrate, the heptahydrate, or the dodecahydrate.

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Monobasic Sodium Phosphate, *USP 26* page 1702 and page 1078 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-24

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate whether it is anhydrous or is the monohydrate or the dihydrate.

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Change to read:

Water, *Method I* ⟨921⟩: less than 2.0% (anhydrous form); between 10.0% and 15.0% (monohydrate); between 18.0% and 26.5% (dihydrate).

■For the monohydrate, the sample may be ground to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results, prior to performing the test.■1S (*USP27*)

Add the following:

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

BRIEFING

Sodium Sulfate, *USP 26* page 1705—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-25

Change to read:

Labeling—Label it to indicate whether it is the decahydrate or is anhydrous.

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

Add the following:

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

BRIEFING

Sodium Thiosulfate, *USP 26* page 1706—See briefing under *Ammonium Chloride.*

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-26

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

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Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Succinylcholine Chloride, *USP 26* page 1716—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-28

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

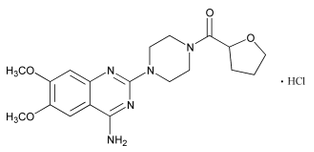
BRIEFING

Terazosin Hydrochloride, page 121 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to revise the current *Packaging and storage* statement to conform to specifications provided by the manufacturer and to those found in *Preservation, Packaging, Storage, and Labeling* under the *General Notices and Requirements*.

(PA5: A. Wilk; PSD: CCO) RTS—40006-1

Add the following:

■Terazosin Hydrochloride



$C_{19}H_{25}N_5O_4 \cdot HCl \cdot 2H_2O$ ~~459.93~~ 459.92

Piperazine, 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)carbonyl]-, monohydrochloride, dihydrate.

1-(4-Amino-6,7-dimethoxy-2-quinazolinyl)-4-(tetrahydro-2-furoyl)piperazine monohydrochloride dihydrate [*70024-40-7*].

Anhydrous 423.89 [*63074-08-8*].

» Terazosin Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{19}H_{25}N_5O_4 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in ~~well-closed containers.~~ tight containers, and store at a temperature between 20° and 25°.

USP Reference standards ⟨11⟩—*USP Terazosin Hydrochloride RS. USP Terazosin Related Compound A RS. USP Terazosin Related Compound ~~E~~ B RS. USP Terazosin Related Compound ~~F~~ C RS.*

In-Process Revision

Color and clarity of solution—Dissolve a quantity of Terazosin Hydrochloride in methanol solution (90 in 100) to obtain a 1 in 100 solution: this solution is clear and colorless to pale yellow, when compared to methanol solution (90 in 100).

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

C: It meets the requirements of the tests for *Chloride* ⟨191⟩, a solution prepared by dissolving 100 mg in 10 mL of methanol solution (90 in 100) being examined.

Loss on drying ⟨731⟩—Dry it in vacuum at 105° for 3 hours: it loses not more than 9.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%, determined on a 1.0-g specimen.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

Limit of tetrahydro-2-furancarboxylic acid—

Blank solution—Transfer 2.0 mL of glacial acetic acid to a 100-mL volumetric flask, dilute with acetone to volume, and mix. Mix 5.0 mL of this solution and 5.0 mL of acetone, pass through a nylon membrane filter having a 0.45-µm or finer porosity, previously washed with acetone, and discard the first 1 mL of the filtrate.

Internal standard solution—Transfer about 100 mg of capric acid, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with acetone to volume, and mix. Transfer 10.0 mL of this solution and 2.0 mL of glacial acetic acid to a 100-mL volumetric flask, dilute with acetone to volume, and mix.

Standard stock solution—Dissolve an accurately weighed amount of tetrahydro-2-furancarboxylic acid in acetone to obtain a solution having a known concentration of about 1.0 mg per mL. Dilute with acetone quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 100 µg per mL.

Standard solution—Transfer 5.0 mL of the *Standard stock solution* and 5.0 mL of *Internal standard solution* to a 50-mL centrifuge tube, and mix. Pass through a nylon membrane filter having a 0.45-µm or finer porosity, previously washed with acetone, and discard the first 1 mL of the filtrate.

Test solution—Transfer about 100 mg of Terazosin Hydrochloride, accurately weighed, to a 50-mL centrifuge tube, add 5.0 mL of acetone and 5.0 mL of *Internal standard solution,* and shake for about 30 minutes. Centrifuge for about 10 minutes, pass through a nylon membrane filter having a 0.45-µm or finer porosity, previously washed with acetone, and discard the first 1 mL of the filtrate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 10-m fused-silica capillary column coated with a 1.2-µm film of liquid phase G25. The column temperature is maintained at about 170°. The injector is configured for splitless injection, and its temperature is maintained at about 230°. The detector temperature is maintained at about 240°. The carrier gas is helium, flowing at a rate of about 9 mL per minute. Chromatograph the *Blank solution,* and measure the peak responses as directed for *Procedure:* ensure that there are no extraneous peaks. Chromatograph the *Standard solution,* and measure the peak responses as directed for *Procedure:* the relative retention times are 1.0 for tetrahydro-2-furancarboxylic acid and 1.2 for capric acid; the resolution, *R,* between tetrahydro-2-furancarboxylic acid and capric acid is not less than 2.3; and the relative standard deviation, determined from the peak response ratios of tetrahydro-2-furancarboxylic acid to capric acid for replicate injections is not more than 6.5%.

Procedure—Separately inject equal volumes (about 0.2 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of tetrahydro-2-furancarboxylic acid in the portion of Terazosin Hydrochloride taken by the formula:

$$100(C/W)(R_U/R_S),$$

in which C is the concentration, in µg per mL, of tetrahydro-2-furancarboxylic acid in the *Standard solution; W* is the weight, in mg, of Terazosin Hydrochloride taken to prepare the *Test solution;* and R_U and R_S are the peak response ratios obtained from the *Test solution* and the *Standard solution,* respectively: not more than ~~0.2%~~ 0.1% is found.

Limit of 1-[(tetrahydro-2-furanyl)carbonyl]piperazine—

Derivatization solution—Dissolve about 2.0 g of 3,5-dinitrobenzoyl chloride in 250 mL of acetonitrile.

Phosphate buffer solution—Transfer about 96.3 g of dibasic potassium phosphate and 3.85 g of monobasic potassium phosphate, each accurately weighed, to a 500-mL volumetric flask. Dissolve in and dilute with water to volume. Adjust with phosphoric acid solution (10 in 100) or sodium hydroxide solution (10 in 100) to a pH of 8.0 ± 0.1. Transfer 25.0 mL of this solution to a 100-mL volumetric flask, and dilute with water to volume. Adjust with phosphoric acid solution (10 in 100) or sodium hydroxide solution (10 in 100) to a pH of 8.0 ± 0.1.

Solution A—Use filtered and degassed water.

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Blank solution—Use acetonitrile.

Standard solution—Dissolve an accurately weighed quantity of 1-[(tetrahydro-2-furanyl)carbonyl]piperazine in acetonitrile to obtain a solution having a known concentration of about 1.0 mg per mL. Dilute quantitatively, and stepwise if necessary, with acetonitrile, to obtain a solution having a known concentration of about 5 µg per mL.

Test solution—Transfer about 125 mg of Terazosin Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with a mixture of acetonitrile and water (1:1) to volume, and mix.

Derivatization procedure—Transfer 5-mL portions of the *Blank solution,* the *Standard solution,* and the *Test solution,* each to a separate 100-mL volumetric flask, and proceed with each as follows. Add 5.0 mL of *Phosphate buffer solution,* and mix. Add 10.0 mL of *Derivatization solution* while swirling, allow to stand at room temperature for about 20 minutes, and mix. Dilute with a mixture of acetonitrile and water (1:1) to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm analytical column that contains packing L7. The flow rate is 1.5 mL per minute, except it is changed to 2.0 mL per minute during the period between 40 and 80 minutes. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–35	82	18	isocratic
35–40	82→10	18→90	linear gradient
40–75	10	90	isocratic
75–80	10→82	90→18	linear gradient
80–100	82	18	isocratic

In-Process Revision

Separately inject equal volumes (about 50 µL) of the derivatized *Blank solution* and the derivatized *Standard solution,* and measure the peak responses as directed for *Procedure,* ensuring that the peaks in the chromatogram of the derivatized *Standard solution* that correspond to those obtained from the derivatized *Blank solution* do not interfere with the determination: the retention time for 1-[(tetrahydro-2-furanyl)carbonyl]piperazine is more than 22 minutes; the column efficiency is not less than 3500 theoretical plates; and the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the derivatized *Standard solution* and the derivatized *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of 1-[(tetrahydro-2-furanyl)carbonyl]piperazine in the portion of Terazosin Hydrochloride taken by the formula:

$$2500(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of 1-[(tetrahydro-2-furanyl)carbonyl]piperazine in the *Standard solution; W* is the weight, in mg, of Terazosin Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak areas for 1-[(tetrahydro-2-furanyl)carbonyl]piperazine derivative obtained from the derivatized *Test solution* and the derivatized *Standard solution*, respectively: not more than 0.1% is found.

Related compounds—

pH 3.2 Citrate buffer, Standard stock preparation, and *Mobile phase*—Proceed as directed in the *Assay.*

Diluent 1—Dissolve 6.0 g of sodium citrate and 4.0 g of anhydrous citric acid in water, dilute with water to 1.0 liter, and mix.

Diluent 2—Prepare a mixture of water, acetonitrile, and methanol (60:30:10).

Standard stock solution 1—Dissolve an accurately weighed quantity of USP Terazosin Related Compound A RS in *Diluent 1*, and dilute with *Diluent 1* to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard stock solution 2—Dissolve an accurately weighed quantity of USP Terazosin Related Compound ~~E~~ B RS in methanol, and dilute with methanol to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard stock solution 3—Dissolve an accurately weighed quantity of USP Terazosin Related Compound ~~F~~ C RS in *Diluent 2*, ~~a mixture of acetonitrile and methanol (1:1),~~ and dilute with *Diluent 2* ~~a mixture of acetonitrile and methanol (1:1)~~ to obtain a solution having a known concentration of about 0.1 mg per mL.

Standard solution—Transfer 5.0 mL of *Standard stock preparation*, 4.0 mL of *Standard stock solution 1*, 4.0 mL of *Standard stock solution 2*, and 20 mL of *Standard stock solution 3* to a 100-mL volumetric flask containing about 60 mL of *Diluent 2*. Dilute with *Diluent 2* to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Use the *Assay stock preparation*.

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *Mobile phase*, and record the peak responses as directed for *Procedure:* ensure that there are no significant interfering peaks. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative retention times are about 0.2 for terazosin related compound A, 1.0 for terazosin, ~~1.94~~ 1.48 for terazosin related compound ~~E~~ B, and 2.57 for terazosin related compound ~~F~~ C; the resolution, R, between terazosin and terazosin related compound ~~E~~ B is not less than 9.0; the column efficiency determined from the terazosin peak is not less than 12,000 theoretical plates; the tailing factor for the terazosin related compound ~~F~~ C peak is not more

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than 3.0; and the relative standard deviation for replicate injections determined from the terazosin peak is not more than 2.0%, and not more than 5.0% determined from the terazosin related compound ~~F~~ C peak.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for about 60 minutes, and measure the peak responses. Separately calculate the quantities, in mg, of terazosin related compound A and terazosin related compound ~~F~~ C in the portion of Terazosin Hydrochloride taken by the formula:

$$200C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution;* and r_U and r_S are the peak responses for the corresponding related compound obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.3% of terazosin related compound A is found; and not more than 0.4% of terazosin related compound ~~F~~ C is found. Calculate the quantity, in mg, of each impurity in the portion of Terazosin Hydrochloride taken by the formula:

$$200C(r_i / r_T),$$

in which C is the concentration, in mg per mL, of USP Terazosin Hydrochloride RS in the *Standard solution;* r_i is the peak response for each impurity, other than terazosin related compound A and terazosin related compound ~~F~~ C, obtained from the *Test solution;* and r_T is the terazosin peak response obtained from the *Standard solution:* not more than 0.3% of any impurity eluting prior to the terazosin peak is found; not more than ~~0.5%~~ 0.1% of any other impurity is found; and not more than ~~1.5%~~ 0.6% of total impurities is found.

Assay—

pH 3.2 Citrate buffer—Dissolve 12.0 g of sodium citrate dihydrate and 28.5 g of anhydrous citric acid in 1.95 liters of water. Adjust with anhydrous citric acid or sodium citrate to a pH of 3.2 ± 0.1. Dilute with water to 2.0 liters, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *pH 3.2 Citrate buffer* and acetonitrile (1685:315). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock preparation—Dissolve an accurately weighed quantity of USP Terazosin Hydrochloride RS in *Mobile phase*, and dilute with *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Standard preparation—Transfer 10.0 mL of *Standard stock preparation* to a 50-mL volumetric flask, and dilute with *Mobile phase* to volume. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Assay stock preparation—Transfer about 100 mg of Terazosin Hydrochloride, accurately weighed, to a 200-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer 10.0 mL of *Assay stock preparation* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer l0.0 mL of this solution to a l00-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The column temperature is maintained at about 30°. The flow rate is about 1.0 mL per minute. Chromatograph the *Mobile phase*, and record the peak responses as directed for *Procedure:* ensure that there are no significant interfering peaks. Chromatograph the *Standard preparation*, and record the peak responses as directed for *Procedure:* the col-

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umn efficiency is not less than 12,000 theoretical plates; the tailing factor is not less than 0.9 and not more than 1.3; and the relative standard deviation for replicate injections is not more than 0.9%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms for about 45 minutes, and measure the peak responses. Calculate the quantity, in mg, of $C_{19}H_{25}N_5O_4 \cdot HCl$ in the portion of Terazosin Hydrochloride taken by the formula:

$$10{,}000C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Terazosin Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation*, respectively.■2S (*USP27*)

BRIEFING

Terbutaline Sulfate, *USP 26* page 1774 and page 2998 of the *First Supplement*—See briefing under *Aminophylline*.

(PA1: K. Russo) RTS—40176-29

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Terbutaline Sulfate RS.* ■*USP Terbutaline Sulfate Related Compound A RS.*■1S (*USP26*)

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Testosterone, *USP 26* page 1781—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-20

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Testosterone RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

■**Other requirements**—Where the label states that Testosterone is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Testosterone Injectable Suspen-*

sion. Where the label states that Testosterone must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Testosterone Injectable Suspension.*■2S (*USP27*)

BRIEFING

Tetracaine Hydrochloride, *USP 26* page 1787—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-30

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Theophylline, *USP 26* page 1801—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-31

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate whether it is hydrous or anhydrous.

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

Change to read:

USP Reference standards ⟨11⟩—*USP Theophylline RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Thiopental Sodium, *USP 26* page 1822—See briefing under *Aminophylline.*

(PA1: K. Russo) RTS—40176-32

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

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Change to read:

USP Reference standards ⟨11⟩—*USP Thiopental RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Tiagabine Hydrochloride, *USP 26* page 1832. It is proposed to change the name of the Reference Standard USP Tiagabine Ethyl Ester Hydrochloride RS to USP Tiagabine Related Compound A RS. This editorial change is reflected in the proposed revision to the test for *Chromatographic purity.* In addition, minor editorial style changes have been made.

(PA3: S. Salado) RTS—39995-1

Change to read:

USP Reference standards ⟨11⟩— ~~*USP Tiagabine Ethyl Ester Hydrochloride RS.*~~

■*USP Tiagabine Related Compound A RS.*■2S (*USP27*)
USP Tiagabine Hydrochloride RS. USP Racemic Tiagabine Hydrochloride Mixture RS.

Change to read:

Chromatographic purity—

Solution A—Use a filtered and degassed solution of water adjusted with phosphoric acid to a pH of 2.3.

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Tiagabine Hydrochloride RS in water to obtain a solution having a known concentration of about 1 mg per mL.

Standard solution—Dilute a portion of the *Standard stock solution* quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.001 mg per mL.

Resolution solution—Dissolve an accurately weighed quantity of ~~USP Tiagabine Ethyl Ester Hydrochloride RS~~

■USP Tiagabine Related Compound A RS■2S (*USP27*)
in water to obtain a solution having a known concentration of about 1 mg per mL. Transfer 1.0 mL of this solution and 1.0 mL of the *Standard stock solution* to a 10-mL volumetric flask, dilute with water to volume, and mix.

Test solution—Transfer about 100 mg of Tiagabine Hydrochloride, accurately weighed, to a 100-mL volumetric flask. Dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	75	25	equilibration
0–30	75→45	25→55	linear gradient
30–40	45→10	55→90	linear gradient
40–45	10	90	isocratic

Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between tiagabine hydrochloride and ~~tiagabine ethyl ester hydrochloride~~

■tiagabine related compound A■2S (*USP27*)
is not less than 9.0; chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Interference check—Inject water as the blank: no interfering peaks are observed.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Tiagabine Hydrochloride taken by the formula:

$$100F(r_i/r_s),$$

in which F is the relative response factor (see the accompanying table for values) for each impurity; r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the sum of the responses of all the peaks, excluding the solvent peaks. (See the accompanying table for limits of individual impurities.) Not more than 1.0% of total impurities is found.

Relative Response Factors

Relative retention time	*F*	Limit (%)
0.51	0.75	0.2
0.79	0.63	0.1
0.93	1.00	0.1
1.13	1.00	0.6
1.32	1.01	0.2
1.39	1.04	0.2
1.98	0.97	0.2
2.27	0.39	0.1
2.33	0.96	0.1
2.54	0.94	0.1
all other peaks	1.00	0.1

BRIEFING

Tolazoline Hydrochloride, *USP 26* page 1852—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-36

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Tolazoline Hydrochloride RS*.

■*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

BRIEFING

Tolbutamide, *USP 26* page 1853—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-27

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Triamcinolone Acetonide, *USP 26* page 1864—See briefing under *Alprostadil*.

(PA1: C. Anthony) RTS—40156-21

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Triamcinolone Acetonide RS*.

■*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Triamcinolone Acetonide is sterile, it meets the requirements for *Sterility and Bacterial endotoxins* under *Triamcinolone Acetonide Injectable Suspension*. Where the label states that

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Triamcinolone Acetonide must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Triamcinolone Acetonide Injectable Suspension*.■2S (*USP27*)

BRIEFING

Trimethobenzamide Hydrochloride, *USP 26* page 1891 and page 672 of *PF* 29(3) [May–June 2003]—See briefing under *Ammonium Chloride*.

(PA4: E. Gonikberg; PSD: C. Okeke) RTS—40204-28

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Trimethobenzamide Hydrochloride RS.*

■*USP Endotoxin RS*.■2S (*USP27*)

Add the following:

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

Change to read:

Assay—Dissolve about 1.3 g of Trimethobenzamide Hydrochloride, previously dried and accurately weighed, in 80 mL of glacial acetic acid and 15 mL of mercuric acetate TS. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically using ~~a calomel-glass electrode system.~~

■suitable electrodes.■1S (*USP27*)
Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 42.49 mg of $C_{21}H_{28}N_2O_5 \cdot HCl$.

BRIEFING

Urea, *USP 26* page 1912. It is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA5: A. Wilk) RTS—40124-37

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Ursodiol Capsules, *USP 26* page 1913. For clarification, it is proposed to include additional information regarding the chromatographic procedure in the *Dissolution* test. Minor editorial style changes have also been made.

(BPC: M. Marques) RTS—40126

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Change to read:

Dissolution ⟨711⟩—

Medium: 0.2 M pH 8.4 phosphate buffer, prepared by mixing 250 mL of 0.2 M monobasic potassium phosphate, 280 mL of 0.2 M potassium hydroxide, and 5 mL of 2% sodium lauryl sulfate solution. Adjust with 0.2 M potassium hydroxide to a pH of 8.4, and dilute with water to 1000 mL; 1000 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Determine the amount of ursodiol dissolved by employing the following method.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and 0.075 M monobasic potassium phosphate (50:50). Adjust with 85% phosphoric acid to a pH of 3.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

■*Standard solution*—Dissolve an accurately weighed quantity of USP Ursodiol RS, and dilute quantitatively, and stepwise if necessary, with *Dissolution Medium* to obtain a solution having a known concentration equivalent to that expected in the solution under test.

Test solution—Use a filtered portion of the solution under test.■2S (*USP27*)

Chromatographic system—The liquid chromatograph is equipped with a refractive index detector, a guard column that contains packing L1, and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1 mL per minute, and the column temperature and detectors are maintained at 40°. ~~Determine the amount of $C_{24}H_{40}O_4$ dissolved.~~

■Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor of the ursodiol peak is not more than 1.7; and the relative standard deviation for replicate injections is not more than 2%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of $C_{24}H_{40}O_4$ dissolved by the formula:

$$100{,}000(r_U / r_S)(C/W),$$

in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively; C is the concentration, in mg per mL, of USP Ursodiol RS in the *Standard solution;* and W is the labeled amount, in mg, of ursodiol in each capsule.■2S (*USP27*)

Tolerances—Not less than 80% *(Q)* of the labeled amount of $C_{24}H_{40}O_4$ is dissolved in 30 minutes.

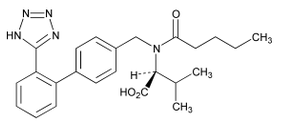
BRIEFING

Valsartan, page 673 of *PF* 29(3) [May–June 2003]. It is proposed to revise the current *Packaging and storage* statement to conform to specifications provided by the manufacturer and to those found in *Preservation, Packaging, Storage, and Labeling* under *General Notices*.

(PA5: A. Wilk; PSD: C. Okeke) RTS—39453-1

Add the following:

■Valsartan



$C_{24}H_{29}N_5O_3$ ~~435.53~~ 435.52

L-Valine, *N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl].

N-[*p*-(*o*-1*H*-Tetrazol-5-yl-phenyl)benzyl]-*N*-valeryl-L-valine [*137862-53-4*].

» Valsartan contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{29}N_5O_3$, calculated on the anhydrous basis.

Packaging and storage—Preserve in ~~well-closed containers.~~ tight containers, and store at 25°; excursions are permitted between 15° and 30°. Protect from moisture and heat.

USP Reference standards ⟨11⟩—*USP Valsartan RS. USP Valsartan Related Compound A RS. USP Valsartan Related Compound B RS. USP Valsartan Related Compound C RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩.

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

Absorbance: not more than ~~0.070~~ 0.07, determined at 420 nm, in a 4-cm cell, on a solution prepared by dissolving 1 g in 20 mL of methanol.

~~**Specific rotation** ⟨781S⟩: between −64° and −69° at 20°.~~

~~*Test solution:* 10 mg per mL, in methanol.~~

Water, *Method I* ⟨921⟩: not more than 2.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Related compounds—

TEST 1 (LIMIT OF VALSARTAN RELATED COMPOUND A)—

~~*0.07 M Phosphate buffer solution*—Dissolve 10.99 g of dibasic sodium phosphate and 3.81 g of monobasic potassium phosphate in water, dilute with water to 1000 mL, and mix.~~

Mobile phase—Prepare a ~~filtered and degassed~~ mixture of ~~*0.07 M Phosphate buffer solution* and isopropyl alcohol (98:2).~~ *n*-hexane, 2-propanol, and trifluoroacetic acid (85:15:0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—~~Pipet 5.0 mL of *System suitability solution* into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Dissolve an accurately weighed quantity of USP Valsartan Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.003 mg of valsartan related compound A per mL.~~ Transfer about 5 mg of USP Valsartan Related Compound A RS, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard solution—Transfer 1.0 mL of *Standard stock solution* into a 10-mL volumetric flask, dilute with *Mobile phase,* and mix. Transfer 1.0 mL of this solution into a 10-mL volumetric flask, dilute with *Mobile phase,* and mix.

System suitability solution—~~Transfer about 30 mg of USP Valsartan Related Compound A, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Mobile phase* to volume. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume (*Solution 1*). Transfer about 15 mg of USP Valsartan RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in *Mobile phase*. Add, by pipetting, 10.0 mL of *Solution 1* to the same flask, dilute with *Mobile phase* to volume, and mix. Dissolve accurately weighed quantities of USP Valsartan RS and USP Valsartan Related Compound A RS in *Mobile phase,* serially diluting, if necessary, to obtain a solution having a known concentration of about 0.15 mg of valsartan per mL and about 0.003 mg of valsartan related compound A per mL.~~ Transfer about 1 mg of Valsartan, accurately weighed, to a ~~20-mL~~ 25-mL volumetric flask, add 10 mL of the *Standard stock solution,* and dissolve in and dilute with *Mobile phase* to volume.

Test solution—~~Transfer about 100 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 5.0 mL of this solution into a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~ Transfer about 50 mg of Valsartan, accurately weighed, to a 50-mL volumetric flask, add about 40 mL of the *Mobile phase,* and sonicate for 5 minutes. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~227-nm~~ 220-nm detector and a ~~4.0-mm × 10-cm~~ 4.6-mm × 25-cm column that contains 5-µm packing ~~L41~~ L40. The flow rate is about 0.8 mL per minute. Chromatograph the *System suit-*

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ability solution, and record the peak responses as directed for *Procedure:* ~~the relative retention times are 0.60 for valsartan related compound A and 1.0 for valsartan; the ratio of the height between the baseline and the lowest point between the valsartan and valsartan related compound A peaks to the height of the valsartan related compound A peak is not more than 0.4. and~~ the resolution, *R,* between valsartan related compound A and valsartan is not less than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation, determined from the valsartan related compound A peaks, for replicate injections is not more than ~~15.0%~~ 5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the ~~heights~~ areas for the major peaks. Calculate the percentage of valsartan related compound A in the portion of Valsartan taken by the formula:

~~$100(r_U/r_S)$,~~

~~in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.5% is found.~~

$$100(C_S/C_U)(r_U/r_S),$$

in which C_S is the concentration, in mg per mL, of USP Valsartan Related Compound A RS in the *Standard solution;* C_U is the concentration, in mg per mL, of valsartan in the *Test solution;* and r_U and r_S are the peak responses for valsartan related compound A obtained from the *Test solution* and *Standard solution,* respectively: not more than ~~1.5%~~ 1.0% is found.

TEST 2 (LIMIT OF VALSARTAN RELATED COMPOUND B, VALSARTAN RELATED COMPOUND C, AND OTHER RELATED COMPOUNDS)—

~~*Diluent* and~~ *Mobile phase*—Proceed as directed in the *Assay.*

~~*Standard stock solution A*—Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase* to obtain a solution having a known concentration of about 5 mg per mL.~~

~~*Standard stock solution B*—Dissolve an accurately weighed quantity of USP Valsartan Related Compound B RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.05 mg per mL.~~

~~*Standard stock solution C*—Dissolve an accurately weighed quantity of USP Valsartan Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.025 mg per mL.~~

Resolution solution—~~Pipet 10.0 mL of *Standard stock solution A*, 5.0 mL of *Standard stock solution B*, and 2.0 mL of *Standard stock solution C* into a 100 mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~ Dissolve accurately weighed quantities of USP Valsartan RS, USP Valsartan Related Compound B RS, and USP Valsartan Related Compound C RS in *Mobile phase,* serially diluting if necessary, to obtain a solution having known concentrations of about ~~0.5 mg~~ 0.001 mg of valsartan per mL, ~~0.0025 mg~~ 0.001 mg of valsartan related compound B per mL, and ~~0.0005 mg~~ 0.001 mg of valsartan related compound C per mL.

Standard solution—~~Dilute an accurately measured volume of *Standard stock solution A* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.0005 mg per mL.~~ Dissolve an accurately weighed quantity of USP Val-

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sartan RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about ~~0.0005 mg~~ 0.001 mg of valsartan per mL.

Test solution—Transfer about 50 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay,* except to use a 225-nm detector. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are 0.73 for valsartan related compound B, 1.0 for valsartan, and 3.8 for valsartan related compound C;~~ the resolution, *R,* between valsartan related compound B and valsartan is not less than 1.8; and the relative standard deviation, determined from the valsartan related compound B peaks, for replicate injections is not more than ~~5.0%~~ 10.0%, and the relative standard deviation, determined from the valsartan peaks, for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Resolution solution,* the *Standard solution,* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of ~~each impurity~~ valsartan related compound B and valsartan related compound C in the portion of Valsartan taken by the formula:

~~$100(Dr_i / r_u)$,~~

~~in which D is the factor due to the extent of dilution and is equal to 2.5 for valsartan related compound B, 0.5 for valsartan related compound C, and 0.05 for all other impurities; r_i is the peak response for each impurity obtained from the *Test solution;* and r_u is the peak response for valsartan related compound B or valsartan related compound C obtained from the *Resolution solution* or the valsartan peak response obtained from the *Standard solution,* as appropriate:~~

$$100(C_S / C_u)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of the appropriate USP Valsartan Related Compound RS in the *Resolution solution;* C_u is the concentration, in mg per mL, of valsartan in the *Test solution;* r_i is the peak response for the impurity obtained from the *Test solution;* and r_S is the peak response for the appropriate valsartan related compound obtained from the *Resolution solution.* Calculate the percentage of each other impurity in the portion of Valsartan taken by the formula:

$$100(C_S / C_u)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Valsartan RS in the *Standard solution;* r_S is the peak response for valsartan obtained from the *Standard solution;* and the other terms are as defined above: not more than ~~0.5%~~ 0.2% of valsartan related compound B is found; not more than 0.1% of valsartan related compound C is found; not more than 0.1% of any other individual impurity, excluding the valsartan related compound A, is found; ~~and not more than 0.5% of total impurities is found.~~ and not more than 0.3% of total impurities, excluding valsartan related compound A, is found.

Assay—

~~*Diluent*—Prepare a mixture of acetonitrile and water (1:1).~~

Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and glacial acetic acid (500:500:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

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Standard preparation—Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about ~~0.05 mg~~ 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. ~~Pipet 10.0 mL of this solution into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~

Chromatographic system—The liquid chromatograph is equipped with a ~~230-nm~~ 248-nm detector and a 3.0-mm × 12.5-cm column that contains 5-µm packing L1. The flow rate is about 0.4 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is between 0.8 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{24}H_{29}N_5O_3$ in the portion of Valsartan taken by the formula:

~~$1000C(r_U/r_S),$~~

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Valsartan RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP27*)

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BRIEFING

Valsartan and Hydrochlorothiazide Tablets, page 1081 of *PF* 29(4) [July–Aug. 2003]. It is proposed to revise the current *Packaging and storage* statement to conform to specifications provided by the manufacturer and to those found in *Preservation, Packaging, Storage, and Labeling* under *General Notices*.

(PA5: A. Wilk; PSD: C. Okeke) RTS—40007-1

Add the following:

■Valsartan and Hydrochlorothiazide Tablets

» Valsartan and Hydrochlorothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

Packaging and storage—Preserve in ~~well-closed containers.~~ tight containers, and store at 25°; excursions are permitted between 15° and 30°. Protect from moisture and heat.

USP Reference standards ⟨11⟩—~~*USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS.*~~ *USP Benzothiadiazine Related Compound A RS. USP Hydrochlorothiazide RS. USP Valsartan RS. USP Valsartan Related Compound B RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—To a centrifuge tube transfer an amount of ground Tablets, equivalent in weight to a single Tablet, add 2.0 mL of acetone, sonicate for 15 minutes, and centrifuge.

Application volume: 2 µL.

Developing solvent system: a mixture of ethyl acetate, dehydrated alcohol, and a solution (25 in 100) of ammonium hydroxide (8:2:1).

Procedure—Proceed as directed in the chapter, except to develop the plate in a paper-lined chromatographic chamber equilibrated with *Developing solvent system* for about 15 minutes prior to use. Allow the chromatogram to develop until the solvent front has moved at least 7 cm. After removing the plate and marking the solvent front, dry the plate under a current of warm air until it is completely dry. The R_F values of the principal spots obtained from the *Test solution* correspond to those obtained from the Standard solution.

B: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 50 rpm.

Time: ~~45~~ 30 minutes.

Procedure—Determine the amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved by employing UV absorption at the wavelengths of maximum absorbance at about 250 nm for valsartan ~~(corrected for interference from hydrochlorothiazide on the basis of the absorbances of hydrochlorothiazide at 250 and 272 nm)~~ and at about 272 nm for hydrochlorothiazide on filtered portions of the solution under test, ~~suitably diluted with *Dissolution Medium,* in comparison with a Standard solution having known concentrations of USP Valsartan RS and USP Hydrochlorothiazide RS in the same *Medium*~~ diluted with *Medium* if necessary. Calculate the quantity of $C_{24}H_{29}N_5O_3$ dissolved, in mg, by the formula:

$$1000D\left(\frac{A_{\text{obs250}}a_{\text{H272}} - A_{\text{obs272}}a_{\text{H250}}}{a_{\text{V250}}a_{\text{H272}} - a_{\text{V272}}a_{\text{H250}}}\right),$$

in which D is the sample dilution factor if used; A_{obs250} is the observed absorbance of the sample solution at 250 nm; A_{obs272} is the observed absorbance of the sample solution at 272 nm; a_{V250} is the absorptivity of valsartan at 250 nm; a_{V272} is the absorptivity of valsartan at 272 nm; a_{H250} is the absorptivity of hydrochlorothiazide at 250 nm; and a_{H272} is the absorptivity of hydrochlorothiazide at 272 nm. The absorptivities, *a,* are determined from separate Standard solutions of USP Valsartan RS and USP Hydrochlorothiazide RS in the *Medium* having known concentration and expressed in units as defined by *Spectrophotometry and Light-Scattering* ⟨851⟩. Calculate the quantity of $C_7H_8ClN_3O_4S_2$ dissolved, in mg, by the formula:

$$1000D\left(\frac{A_{\text{obs272}}a_{\text{V250}} - A_{\text{obs250}}a_{\text{V272}}}{a_{\text{V250}}a_{\text{H272}} - a_{\text{V272}}a_{\text{H250}}}\right),$$

in which the terms are as defined above.

Tolerances—Not less than ~~75%~~ 80% *(Q)* of the labeled amounts of $C_{24}H_{29}N_5O_3$ and $C_7H_8ClN_3O_4S_2$ is dissolved in ~~45~~ 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Diluent, Solution A, Solution B, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

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

Test solution—Place 1 Tablet in a 200-mL volumetric flask, add 5 mL of water, and allow to stand for 5 minutes. Add about 100 mL of *Diluent,* and sonicate for 15 minutes. Dilute with *Diluent* to volume, mix, and centrifuge a portion of this solution at about 3000 rpm. Quantitatively dilute a volume of the clear supernatant with *Diluent* to obtain a solution having a concentration of about 0.2 mg of valsartan per mL.

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Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the quantities, in mg, of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the Tablet taken by the formula:

$$(LC_S / C_U)(r_U / r_S),$$

in which L is the labeled quantity, in mg, of the relevant analyte in the Tablet; C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution;* C_U is the concentration, in mg per mL, of the corresponding analyte in the *Test solution,* based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Related compounds—

Diluent, Solution A, Solution B, and *Mobile phase*—Prepare as directed in the *Assay.*

Standard stock solution—Dissolve accurately weighed quantities of ~~USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS,~~ USP Benzothiadiazine Related Compound A RS, USP Hydrochlorothiazide RS, USP Valsartan RS, and USP Valsartan Related Compound B RS in *Diluent* to obtain a solution having known concentrations of about 0.03 mg per mL, 0.06 mg per mL, 0.08 mg per mL, and 0.2 mg per mL, respectively.

Resolution solution—Dilute 5.0 mL of *Standard stock solution* with *Diluent* to 100.0 mL, and mix.

Standard solution—Dilute 10.0 mL of *Resolution solution* with *Diluent* to 100.0 mL, and mix.

Test solution—Use the *Assay preparation* as specified.

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between valsartan related compound B and valsartan, and between ~~4-amino-6-chloro-1,3-benzenedisulfonamide~~ benzothiadiazine related compound A and hydrochlorothiazide is not less than 1.4. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation, determined from the valsartan and hydrochlorothiazide peaks, for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks, disregarding the peak, if any, with a retention time of about 22 minutes. Calculate the quantity, in mg, of each impurity in the portion of Tablets taken by the formula:

$$2000C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of ~~USP Valsartan Related Compound B RS or USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS,~~ USP Benzothiadiazine Related Compound A RS, or the relevant USP Reference Standard (when determining the quantity of other impurities) in the *Standard solution;* and r_U and r_S are the corresponding peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than ~~0.5%~~ 1.0% ~~each of valsartan related compound B and~~ of ~~4-amino-6-chloro-1,3-benzenedisulfonamide~~ benzothiadiazine related compound A is found; not more than 0.2% of any other impurity, excluding valsartan related compound A and valsartan re-

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lated compound B, is found; and not more than ~~0.8%~~ 1.3% of total impurities, excluding valsartan related compound A and valsartan related compound B, is found. [NOTE—Valsartan related compound A is the enantiomer of valsartan and coelutes with valsartan in this test.]

Assay—

Diluent—Prepare a mixture of acetonitrile and water (1:1).

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (90:10:0.1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, water, and trifluoroacetic acid (90:10:0.1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 12.5 mg of USP Hydrochlorothiazide RS, accurately weighed, to a 200-mL volumetric flask. Add about 12.5*J* mg of USP Valsartan RS, accurately weighed, *J* being the ratio of the labeled amount, in mg, of valsartan to the labeled amount, in mg, of hydrochlorothiazide per Tablet. Add about 100 mL of *Diluent*, sonicate for 15 minutes, dilute with *Diluent* to volume, and mix. Transfer 25.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Quantitatively dilute a volume of this solution with *Diluent* to obtain a solution having a known concentration of about 0.2 mg of USP Valsartan RS per mL.

Assay preparation—Transfer a number of Tablets, equivalent to about 62.5 mg of hydrochlorothiazide, to a 250-mL volumetric flask. Add 5 mL of water, and allow to stand for 5 minutes. Then add about 100 mL of *Diluent*, sonicate for 15 minutes, and shake for 30 minutes. Dilute with *Diluent* to volume, mix, and centrifuge a portion of this solution at 3000 rpm. Dilute 25.0 mL of the clear supernatant with *Diluent* to 200.0 mL, and mix *(Solution 1).* [NOTE—Retain a portion of *Solution 1* to use as the *Test solution* in the test for *Related compounds*.] Dilute an accurately measured volume of *Solution 1* with *Diluent* to obtain a solution containing about 0.2 mg of valsartan per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 265-nm detector and a 3.0-mm × 12.5-cm column that contains 5-µm packing L1. The flow rate is about 0.4 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–25	90→10	10→90	linear gradient
25–27	10→90	90→10	linear gradient
27–40	90	10	isocratic

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the quantities, in mg, of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken by the formula:

$$(LC_S / C_U)(r_U / r_S),$$

in which L is the labeled quantity, in mg, of the relevant analyte in each Tablet; C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard preparation;* C_U is the concentration, in mg per mL, of the corresponding analyte in the *Assay preparation,* based on the labeled quantity per Tablet and the extent of dilution;

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and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Verapamil Hydrochloride, *USP 26* page 1924—See briefing under *Amifostine*.

(PA5: A. Wilk) RTS—40124-38

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Verapamil Hydrochloride RS. USP Verapamil Related Compound B RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

MONOGRAPHS (NF)

BRIEFING

Benzyl Alcohol, *NF 21* page 2698 and page 879 of *PF* 28(3) [May–June 2002]. It is proposed to delete the requirement to ignite the sample to constant weight in the *Residue on ignition* test. This will make it clear that the sample is ignited to constant weight only if compliance with the monograph limit is not obtained first, as provided in the general test chapter *Residue on Ignition* ⟨281⟩.

(EMC: D. Bempong) RTS—40195-1

Change to read:

Residue on ignition ⟨281⟩—Evaporate 25 mL in a suitable crucible, and ignite: ~~to constant weight.~~

■■2S (*NF22*)
not more than 0.005% is found.

BRIEFING

Butylparaben, *NF 21* page 2701; **Ethylparaben,** *NF 21* page 2745; **Propylparaben,** *NF 21* page 2824; **Methylparaben,** *NF 21* page 2794. On the basis of comments received, it is proposed to change the specification range in the Definition and to revise the operating conditions in the *Assay* based on the *Assay* appearing in the harmonization draft proposals on pages 1967–1970 of *PF* 28(6) [Nov.–Dec. 2002] and page 575 of *PF* 28(2) [Mar.–Apr. 2002], respectively. In the *Assay*, it is proposed to reduce the sample weight, to change the heating process to give a specific temperature, and to omit the reflux step. Interested parties are encouraged to submit comments.

(EMC: C. Sheehan) RTS—40159-1

Change to read:

» Butylparaben contains not less than ~~99.0 percent~~

■98.0 percent■2S (*NF22*)
and not more than ~~100.5 percent~~

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■102.0 percent■2S *(NF22)*
of $C_{11}H_{14}O_3$, calculated on the dried basis.

Change to read:

Assay— ~~Transfer about 2 g of Butylparaben, accurately weighed, to a flask fitted with a ground-glass stopper and equipped for refluxing under a water-cooled condenser. Add 40.0 mL of 1 N sodium hydroxide VS, and reflux for 1 hour. Cool to room temperature, and rinse the condenser with water.~~

■Transfer about 1 g of Butylparaben, accurately weighed, to a flask fitted with a ground-glass stopper. Add 20.0 mL of 1 N sodium hydroxide VS, and heat at about 70° for 1 hour. Cool rapidly in an ice bath. Carry out the titration of the solutions at room temperature.■2S *(NF22)*
Titrate the excess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 1 N sodium hydroxide is equivalent to 194.2 mg of $C_{11}H_{14}O_3$.

BRIEFING

Ethylparaben, *NF 21* page 2745 and page 1968 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Butylparaben.*

(EMC: C. Sheehan) RTS—40160-1

Change to read:

» Ethylparaben contains not less than ~~99.0 percent~~

■98.0 percent■2S *(NF22)*
percent and not more than ~~100.5 percent~~

■102.0 percent■2S *(NF22)*
of $C_9H_{10}O_3$, calculated on the dried basis.

Change to read:

Assay— ~~Proceed with Ethylparaben as directed in the *Assay* under *Butylparaben.* Each mL of 1 N sodium hydroxide is equivalent to 166.2 mg of $C_9H_{10}O_3$.~~

■Transfer about 1 g of Ethylparaben, accurately weighed, to a flask fitted with a ground-glass stopper. Add 20.0 mL of 1 N sodium hydroxide VS, and heat at about 70° for 1 hour. Cool rapidly in an ice bath. Carry out the titration of the solutions at room temperature. Titrate the excess sodium hydroxide with 0.5 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 1 N sodium hydroxide is equivalent to 166.2 mg of $C_9H_{10}O_3$.■2S *(NF22)*

BRIEFING

Methylparaben, *NF 21* page 2794 and page 575 of *PF* 28(2) [Mar.–Apr. 2002]—See briefing under *Butylparaben*.

(EMC: C. Sheehan) RTS—40161-1

Change to read:

» Methylparaben contains not less than ~~99.0 percent~~

■98.0 percent■2S *(NF22)*
and not more than ~~100.5 percent~~

■102.0 percent■2S *(NF22)*
of $C_8H_8O_3$.

Change to read:

Assay— ~~Transfer about 2 g of Methylparaben, accurately weighed, to a flask fitted with a ground-glass stopper and equipped for refluxing under a water-cooled condenser. Add 40.0 mL of 1 N sodium hydroxide VS, and reflux for 1 hour. Cool to room temperature, and rinse the condenser with water. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS,~~

■Transfer about 1 g of Methylparaben, accurately weighed, to a flask fitted with a ground-glass stopper. Add 20.0 mL of 1 N sodium hydroxide VS, and heat at about 70° for 1 hour. Cool rapidly in an ice bath. Carry out the titration of the solutions at room temperature. Titrate the excess sodium hydroxide with 0.5 N sulfuric acid VS,■2S *(NF22)*
continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 1 N sodium hydroxide is equivalent to 152.2 mg of $C_8H_8O_3$.

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BRIEFING

Mono- and Di-glycerides, *NF 21* page 2798 and page 3024 of the *First Supplement*. On the basis of comments received that the relative retention times in the *Assay for monoglycerides* are too restrictive, it is proposed to replace the approximate relative retention times specified in the test with the order of elution of the expected components. Also, because the precision involved in *Iodine value* determination could lead to failure problems for monograph items that have low iodine values, it is proposed to revise the test to reflect a new requirement for items with a nominal iodine value less than 10.

(EMC: D. Bempong) RTS—39818-1

Change to read:

Iodine value ⟨401⟩: not less than 90.0% and not more than 110.0% of the value indicated in the labeling.

■If the value stated in the labeling is less than 10, the *Iodine value* is not more than 10.■2S (*NF22*)

Change to read:

Assay for monoglycerides—

Mobile phase—Use filtered and degassed tetrahydrofuran. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Assay preparation—Transfer about 200 mg of Mono- and Di-glycerides, accurately weighed, to a 5-mL volumetric flask, dissolve in and dilute with tetrahydrofuran to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and a 7-mm × 60-cm column that contains ■5-µm■1S (*NF21*) packing L21 ■(100 Å).■1S (*NF21*) The flow rate is about 1 mL per minute. The column and detector temperatures are maintained at 40°. Chromatograph the *Assay preparation,* and record the peak responses as directed for *Procedure*. ~~the relative retention times are about 1.0 for glycerin, 0.86 for monoglycerides, 0.81 for diglycerides, and 0.77 for triglycerides; and~~

■The order of elution is triglycerides, diglycerides, monoglycerides, and glycerin.■2S (*NF22*)

The relative standard deviation for replicate injections determined from the monoglycerides peak is not more than 1.0%.

Procedure—Inject a volume (about 40 µL) of the *Assay preparation* into the chromatograph, record the chromatogram, and measure the responses for the major peaks. Calculate the percentage of monoglycerides in the portion of Mono- and Di-glycerides taken by the formula:

$$100(r_U/r_s),$$

in which r_U is the peak response for monoglycerides; and r_s is the sum of the responses of all the peaks, except the solvent peak.

BRIEFING

Propylparaben, *NF 21* page 2824 and page 1970 of *PF* 28(6) [Nov.–Dec. 2002]—See briefing under *Butylparaben.*

(EMC: C. Sheehan) RTS—40162-1

Change to read:

» Propylparaben contains not less than ~~99.0 percent~~ ■98.0 percent■2S (*NF22*) and not more than ~~100.5 percent~~ ■102.0 percent■2S (*NF22*) of $C_{10}H_{12}O_3$, calculated on the dried basis.

Change to read:

Assay— ~~Proceed with Propylparaben as directed in the *Assay* under *Butylparaben*. Each mL of 1 N sodium hydroxide is equivalent to 180.2 mg of $C_{10}H_{12}O_3$.~~

■Transfer about 1 g of Propylparaben, accurately weighed, to a flask fitted with a ground-glass stopper. Add 20.0 mL of 1 N sodium hydroxide VS, and heat at about 70° for 1 hour. Cool rapidly in an ice bath. Carry out the titration of the solutions at room temperature. Titrate the excess sodium hydroxide with 1 N sulfuric acid VS, continuing the titration until the second point of inflection and determining the endpoint potentiometrically (see *Titrimetry* ⟨541⟩). Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 1 N sodium hydroxide is equivalent to 180.2 mg of $C_{10}H_{12}O_3$.■2S (*NF22*)

BRIEFING

Pregelatinized Starch, *NF 21* page 2843 and page 706 of *PF* 29(3) [May–June 2003]. This monograph is being presented again with changes to the *Packaging and storage* section and to the tests for *Identification* and *Microbial limits*. The *Packaging and storage* statement has been revised to incorporate storage specifications provided by a manufacturer. The *Identification* test has been changed to be consistent with the Adoption Stage 6 harmonization pro-

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posals for the Starch monographs. It is proposed to include the requirements for total aerobic microbial count and total combined molds and yeasts count under *Microbial limits*.

(EMC: C. Sheehan; PSD: C. Okeke; AMB: D. Porter)
RTS—40158-1

Add the following:

■**Packaging and storage**—Preserve in ~~well closed~~ tight containers. Store at 25°, excursions permitted up to 40°.■2S (*NF22*)

Add the following:

■**Labeling**—Label it to indicate the botanical source from which it was derived.■2S (*NF22*)

Add the following:

■**Identification**—A water slurry of it is colored ~~reddish violet~~ orange red to deep blue by iodine TS.■2S (*NF22*)

Add the following:

■**Microbial limits** ⟨61⟩—It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*. The total aerobic microbial count does not exceed 10^3 cfu per g, and the total combined molds and yeasts count does not exceed 10^2 cfu per g.■2S (*NF22*)

Add the following:

■**Loss on drying** ⟨731⟩—Dry it at 120° for 4 hours: it loses not more than 14.0% of its weight.■2S (*NF22*)

Add the following:

■**Residue on ignition** ⟨281⟩: not more than 0.5%, determined on a 2.0-g test specimen.■2S (*NF22*)

Change to read:

Sulfur dioxide—Mix 20 g with 200 mL of a 1 in 5 solution of anhydrous sodium sulfate, and filter. To 100 mL of the clear filtrate add 3 mL of starch TS, and titrate with ~~0.010 N iodine~~

■0.01 N iodine VS■1S (*NF22*)
to the first permanent blue color: not more than 2.7 mL is consumed (0.008%).

Delete the following:

■~~**Other requirements**—It responds to *Identification* test *B* and meets the requirements for *Packaging and storage, Labeling, Microbial limits, Loss on drying,* and *Residue on ignition* under *Starch.*~~■2S (*NF22*)

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**11**⟩ **Reference Standards,** *USP 26* page 1966, page 3131 of the *Second Supplement,* page 3212 of *PF* 22(6) [Nov.–Dec. 1996], page 4500 of *PF* 23(4) [July–Aug. 1997], page 5180 of *PF* 23(6) [Nov.–Dec. 1997], page 6925 of *PF* 24(5) [Aug.–Sept. 1998], page 8222 of *PF* 25(3) [May–June 1999], page 8561 of *PF* 25(4) [July–Aug. 1999], page 8893 of *PF* 25(5) [Sept.–Oct. 1999], page 9222 of *PF* 25(6) [Nov.–Dec. 1999], page 218 of *PF* 26(1) [Jan.–Feb. 2000], page 471 of *PF* 26(2) [Mar.–Apr. 2000], page 793 of *PF* 26(3) [May–June 2000], page 1369 of *PF* 26(5) [Sept.–Oct. 2000], page 1606 of *PF* 26(6) [Nov.–Dec. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 2268 of *PF* 27(2) [Mar.–Apr. 2001], page 2594 of *PF* 27(3) [May–June 2001], page 2806 of *PF* 27(4) [July–Aug. 2001], page 3071 of *PF* 27(5) [Sept.–Oct. 2001], page 3348 of *PF* 27(6) [Nov.–Dec. 2001], page 111 of *PF* 28(1) [Jan.–Feb. 2002], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 839 of *PF* 28(3) [May–June 2002], page 1224 of *PF* 28(4) [July–Aug. 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 1913 of *PF* 28(6) [Nov.–Dec. 2002], page 163 of *PF* 29(1) [Jan.–Feb. 2003], page 483 of *PF* 29(2) [Mar.–Apr. 2003], page 710 of *PF* 29(3) [May–June 2003], and page 1137 of *PF* 29(4) [July–Aug. 2003].

(HDQ) RTS—38539-2; 37377-1; 39377-2; 38976-1; 39471-2; 39640-4; 39903-1; 39985-2; 39995-2; 40056-2; 40038-3; 40078-1

Add the following:

■**USP Alcohol Determination—Acetonitrile RS**—[To come.]■2S (*USP27*)

Add the following:

■**USP Alcohol Determination—Alcohol RS**—[To come.]■2S (*USP27*)

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Add the following:

■**USP Benazepril Related Compound A RS** ~~[3-(1-ethoxycarbonyl-3-phenyl-(1*R*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*R*)-benazepine)-1-acetic acid]~~ (3*R*) 3-[[(1*R*) 1-(ethoxycarbonyl)-3-phenylpropyl] amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benazapine-1-acetic acid, monohydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$ ✧ ~~460.96~~ 460.95)—Do not dry. Store in a refrigerator. Protect from light.■2S (*USP27*)

Add the following:

■**USP Benazepril Related Compound B RS** ~~[3-(1-ethoxycarbonyl-3-phenyl-(1*R*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benazepine)-1-acetic acid]~~ (3*S*) 3-[[(1*R*) 1-(ethoxycarbonyl)-3-phenylpropyl] amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benazapine-1-acetic acid, monohydrochloride ($C_{24}H_{28}N_2O_5 \cdot HCl$ ✧ ~~460.96~~ 460.95)—Do not dry. Store in a refrigerator. Protect from light.■2S (*USP27*)

Add the following:

■**USP Calcitrol RS**—Store in a refrigerator. Protect from light.■2S (*USP27*)

Add the following:

■**USP Calcitrol Solution RS**—Store in a refrigerator. Protect from light.■2S (*USP27*)

Add the following:

■**USP Clopidogrel Bisulfate RS**—[To come.]■2S (*USP27*)

Add the following:

■**USP Clopidogrel Related Compound A RS** **[**(+)-(*S*)-(*o*-chlorophenyl)-6,7-dihydrothienol[3,2,*c*]pyridine-5(4*H*)-acetic acid**]**—[To come.]■2S (*USP27*)

Add the following:

■**USP Clopidogrel Related Compound B RS** **[**Methyl (±)-(*o*-chlorophenyl)-6,7-dihydrothieno[3,2,*c*]pyridine-5(4*H*)-acetate, hydrogen sulfate**]**—[To come.]■2S (*USP27*)

Add the following:

■**USP Clopidogrel Related Compound C RS** **[**Methyl (–)-(*R*)-*o*-chlorophyenyl)-6,7-dihydrothieno[3,2,*c*]pyridine-5(4*H*)-acetate, hydrogen sulfate**]**—[To come.]■2S (*USP27*)

Change to read:

USP Flumazenil RS—

■Do not dry; determine the water content titrimetrically at the time of use. Keep container tightly closed.■2S (*USP27*)

Add the following:

■**USP Flumazenil Related Compound A RS**—**[**8-fluoro-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazol-[1,5-*a*][1,4]benzodiazepine-3-carboxylic acid**]** ($C_{13}H_{10}FN_3O_3$ ✧ 275.24)—[To come.]■2S (*USP27*)

Add the following:

■**USP Flumazenil Related Compound B RS**—**[**Ethyl 8-hydroxy-5,6-dihydro-5-methyl-6-oxo-4*H*-imidazol-[1,5-*a*][1,4]benzodiazepine-3-carboxylate**]** ($C_{15}H_{15}N_3O_4$ ✧ 301.30)—[To come.]■2S (*USP27*)

Add the following:

■**USP Hexafluoroisopropanol RS** **[**1,1,1,3,3,3-hexafluoro-2-propanol**]**—Do not dry.■2S (*USP27*)

Add the following:

■**USP Isosorbide Mononitrate RS.**■2S (*USP27*)

Add the following:

■**USP Isosorbide Mononitrate Related Compound A RS** **[**1,4:3,5-Dianhydro-D-glucitol 2-nitrate**]** ($C_6H_9NO_6$ ✧ 191.14).■2S (*USP27*)

Add the following:

■**USP Mefloquine Hydrochloride RS.**■2S (*USP27*)

Add the following:

■**USP Metronidazole Benzoate RS**—Dry at 80° for 3 hours.■2S (*USP27*)

Add the following:

■**USP Ondansetron Resolution Mixture RS**—Ondansetron hydrochloride having approximately 0.4% w/w of both ondansetron related compound A and 6,6′-methylene bis-[(1,2,3,9-tetrahydro-9-methyl-3-[(2-methyl-1*H*-imidazol-1-yl)-methyl]-4*H*-carbazol-4-one)].■2S (*USP27*)

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Add the following:

■**USP Paroxetine Related Compound D RS** [*cis*-paroxetine hydrochloride]—Do not dry.■2S (*USP27*)

Add the following:

■**USP Sevomethyl Ether RS** [1,1,1,3,3,3-hexafluoro-2-methoxy-propane]—Do not dry.■2S (*USP27*)

Change to read:
▲**USP Tiagabine ~~Ethyl Ester Hydrochloride~~**

■**Related Compound A**■2S (*USP27*)
RS [(*R*)-ethyl 1-[4,4-bis(3-methyl-2-thienyl)-3-butenyl]-3-piperidinecarboxylate] ($C_{22}H_{29}NO_2S_2 \cdot HCl$ ✧ 440.0)—Do not dry.▲*USP26*

Chemical Tests and Assays

LIMIT TESTS

BRIEFING

⟨**231**⟩ **Heavy Metals,** *USP 26* page 2057 and page 1570 of *PF* 28(5) [Sept.–Oct. 2002]. On the basis of comments received, the use of a pH meter to adjust the pH in *Method I* and *Method III* is proposed. Situations in which the *Monitor Preparation* has a lighter color than the *Standard Preparation* have been reported. This problem could indicate that the pH is out of range, and external pH short-range paper indicators may not be accurate enough to detect this change. In addition to these changes, and to be consistent with *Methods I* and *II*, a formula to calculate the amount of substance to be tested is added in *Method III*.

Method II also reflects changes to the USP test appearing under the harmonization section (see page 1570 of *PF* 28(5) [Sept.–Oct 2002]). These changes are based on suggestions made in a *Stimuli* article by K. B. Blake entitled *Harmonization of the USP, EP, and JP Heavy Metals Testing Procedures* (see page 1632 of *PF* 21(6) [Nov.–Dec. 1995]). The Blake article concludes that the ashing process in *Method II* is responsible for a loss of as much as 100% of mercury content and up to 50% of the heavy metals present. Improvements in heavy metal limit determination by *Method II* are expected following the inclusion of a *Monitor Preparation,* an increase in the amount of sample, and a corresponding increase in the amount of lead in both the *Standard Preparation* and the *Monitor Preparation*. The *Monitor Preparation* is intended as a means of validating the use of *Method II,* with the instruction to proceed to *Method III* if the solution from the *Monitor Preparation* is less colored than the solution from the *Standard Preparation*.

Comments regarding this proposal are invited and should be submitted by March 15, 2004.

(PA6: H. Pappa) RTS—39947-1; 39948-1

Change to read:

Method I

pH 3.5 Acetate Buffer—Dissolve 25.0 g of ammonium acetate in 25 mL of water, and add 38.0 mL of 6 N hydrochloric acid. Adjust, if necessary, with 6 N ammonium hydroxide or 6 N hydrochloric acid to a pH of 3.5, dilute with water to 100 mL, and mix.

Standard Preparation—Into a 50-mL color-comparison tube pipet 2 mL of *Standard Lead Solution* (20 µg of Pb), and dilute with water to 25 mL. ~~Adjust~~

■Using a pH meter, adjust■2S (*USP27*) with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, ~~using short-range pH indicator paper as external indicator,~~

■■2S (*USP27*) dilute with water to 40 mL, and mix.

Test Preparation—Into a 50-mL color-comparison tube place 25 mL of the solution prepared for the test as directed in the individual monograph; or, using the designated volume of acid where specified in the individual monograph, dissolve and dilute with water to 25 mL the quantity, in g, of the substance to be tested, as calculated by the formula:

$$2.0/(1000L),$$

in which L is the *Heavy metals* limit, ~~in percentage. Adjust~~

■as a percentage. Using a pH meter, adjust■2S (*USP27*) with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, ~~using short-range pH indicator paper as external indicator,~~

■■2S (*USP27*) dilute with water to 40 mL, and mix.

Monitor Preparation—Into a third 50-mL color-comparison tube place 25 mL of a solution prepared as directed for *Test Preparation,* and add 2.0 mL of *Standard Lead Solution.* ~~Adjust~~

■Using a pH meter, adjust■2S (*USP27*) with 1 N acetic acid or 6 N ammonium hydroxide to a pH between 3.0 and 4.0, ~~using short-range pH indicator paper as external indicator,~~

■■2S (*USP27*) dilute with water to 40 mL, and mix.

Procedure—To each of the three tubes containing the *Standard Preparation,* the *Test Preparation,* and the *Monitor Preparation,* add 2 mL of *pH 3.5 Acetate Buffer,* then add 1.2 mL of thioacetamide-glycerin base TS, dilute with water to 50 mL, mix, allow to stand for 2 minutes, and view downward over a white surface*: the color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation,* and ~~the intensity of~~ the color of the

* In those countries or jurisdictions where thioacetamide cannot be used, add 10 mL of freshly prepared hydrogen sulfide TS to each of the tubes, mix, allow to stand for 5 minutes, and view downward over a white surface.

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■solution from the■2S (*USP27*)
Monitor Preparation is equal to or ~~greater~~

■darker■2S (*USP27*)
than that of the

■solution from the■2S (*USP27*)
Standard Preparation. [NOTE—If the color of the *Monitor Preparation* is lighter than that of the *Standard Preparation,* use *Method II* instead of *Method I* for the substance being tested.]

Change to read:

Method II

pH 3.5 Acetate Buffer—Prepare as directed for *Method I.*
Standard Preparation—~~Prepare as directed under *Method I.*~~

■Pipet 4 mL of the *Standard Lead Solution* into a suitable test tube, and add 10 mL of 6 N hydrocloric acid.■2S (*USP27*)

Test Preparation—Use a quantity, in g, of the substance to be tested as calculated by the formula:

~~2.0/(1000*L*),~~

■4.0/(1000*L*),■2S (*USP27*)

in which *L* is the *Heavy metals* limit, ~~in~~

■as a■2S (*USP27*)
percentage. Transfer the weighed quantity of the substance to a suitable crucible, add sufficient sulfuric acid to wet the substance, and carefully ignite at a low temperature until thoroughly charred. (The crucible may be loosely covered with a suitable lid during the charring.) Add to the carbonized mass 2 mL of nitric acid and 5 drops of sulfuric acid, and heat cautiously until white fumes no longer are evolved. Ignite, preferably in a muffle furnace, at 500° to 600°, until the carbon is completely burned off

■(no longer than 2 hours). If carbon remains, allow the residue to cool, add a few drops of sulfuric acid, evaporate, and ignite again.■2S (*USP27*)
Cool, add ~~4 mL~~

■5 mL■2S (*USP27*)
of 6 N hydrochloric acid, cover,

■and■2S (*USP27*)
digest on a steam bath for ~~15 minutes, uncover, and slowly evaporate on a steam bath to dryness. Moisten the residue with 1 drop of hydrochloric acid, add 10 mL of hot water, and digest for 2 minutes. Add 6 N ammonium hydroxide dropwise, until the solution is just alkaline to litmus paper, dilute with water to 25 mL, and adjust with 1 N acetic acid to a pH between 3.0 and 4.0, using short-range pH indicator paper as external indicator. Filter if necessary, rinse the crucible and the filter with 10 mL of water, combine the filtrate and rinsing in a 50-mL color-comparison tube, dilute with water to 40 mL, and mix.~~

■10 minutes. Cool, and quantitatively transfer the solution to a test tube. Rinse the crucible with a second 5-mL portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube.

Monitor Preparation—Pipet 4 mL of the *Standard Lead Solution* into a crucible identical to that used for the *Test Preparation* and containing a quantity of the substance under test that is equal to 10% of the amount required for the *Test Preparation*. Evaporate on a steam bath to dryness. Ignite at the same time, in the same muffle furnace, and under the same conditions used for the *Test Preparation*. Cool, add 5 mL of 6 N hydrochloric acid, cover, and digest on a steam bath for 10 minutes. Cool, and quantitatively transfer to a test tube. Rinse the crucible with a second 5-mL portion of 6 N hydrochloric acid, and transfer the rinsing to the test tube.■2S (*USP27*)

Procedure—~~To~~

■Adjust the solution in■2S (*USP27*)
each of the tubes containing the *Standard Preparation,*~~and~~ the *Test Preparation,*

■and the *Monitor Preparation* with ammonium hydroxide, added cautiously and dropwise, to a pH of 9. Cool, and adjust with glacial acetic acid, added dropwise, to a pH of 8, and then add 0.5 mL in excess. Filter, washing the filter with a few mL of water, into a 50-mL color-comparison tube, and then dilute with water to 40 mL.■2S (*USP27*)

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Add 2 mL of *pH 3.5 Acetate Buffer,* then add 1.2 mL of thioacetamide-glycerin base TS, dilute with water to 50 mL, mix, allow to stand for 2 minutes, and view downward over a white surface*: the color of the solution from the *Test Preparation* is not darker than that of the solution from the *Standard Preparation,*

■and the color of the solution from the *Monitor Preparation* is equal to or darker than that of the solution from the *Standard Preparation*. [NOTE—If the color of the solution from the *Monitor Preparation* is lighter than that of the solution from the *Standard Preparation,* proceed as directed for *Method III* for the substance being tested.]■2S (*USP27*)

Change to read:

Method III

pH 3.5 Acetate Buffer—Prepare as directed for *Method I.*

Standard Preparation—Transfer a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to a clean, dry, 100-mL Kjeldahl flask, and add a further volume of nitric acid equal to the incremental volume of nitric acid added to the *Test Preparation.* Heat the solution to the production of dense, white fumes, cool, cautiously add 10 mL of water and, if hydrogen peroxide was used in treating the *Test Preparation,* add a volume of 30 percent hydrogen peroxide equal to that used for the substance being tested, and boil gently to the production of dense, white fumes. Again cool, cautiously add 5 mL of water, mix, and boil gently to the production of dense, white fumes and to a volume of 2 to 3 mL. Cool, dilute cautiously with a few mL of water, add 2.0 mL of *Standard Lead Solution* (20 µg of Pb), and mix. Transfer to a 50-mL color-comparison tube, rinse the flask with water, adding the rinsing to the tube until the volume is 25 mL, and mix.

Test Preparation—

■Unless otherwise indicated in the individual monograph, use a quantity, in g, of the substance to be tested as calculated by the formula:

$$2.0/(1000L),$$

in which L is the *Heavy metals* limit, as a percentage.■2S (*USP27*)

If the substance is a solid—Transfer the

■weighed■2S (*USP27*) quantity of the test substance ~~specified in the individual monograph~~

■■2S (*USP27*) to a clean, dry, 100-mL Kjeldahl flask. [NOTE—A 300-mL flask may be used if the reaction foams excessively.] Clamp the flask at an angle of 45°, and add a sufficient quantity of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid to moisten the substance thoroughly. Warm gently until the reaction commences, allow the reaction to subside, and add additional portions of the same acid mixture, heating after each addition, until a total of 18 mL of the acid mixture has been added. Increase the amount of heat, and boil gently until the solution darkens. Cool, add 2 mL of nitric acid, and heat again until the solution darkens. Continue the heating, followed by addition of nitric acid until no further darkening occurs, then heat strongly to the production of dense, white fumes. Cool, cautiously add 5 mL of water, boil gently to the production of dense, white fumes, and continue heating until the volume is reduced to a few mL. Cool, cautiously add 5 mL of water, and examine the color of the solution. If the color is yellow, cautiously add 1 mL of 30 percent hydrogen peroxide, and again evaporate to the production of dense, white fumes and a volume of 2 to 3 mL. If the solution is still yellow in color, repeat the addition of 5 mL of water and the peroxide treatment. Cool, dilute cautiously with a few mL of water, and rinse into a 50-mL color-comparison tube, taking care that the combined volume does not exceed 25 mL.

If the substance is a liquid—Transfer the

■weighed■2S (*USP27*) quantity of the test substance ~~specified in the individual monograph~~

■■2S (*USP27*) to a clean, dry, 100-mL Kjeldahl flask. [NOTE—A 300-mL flask may be used if the reaction foams excessively.] Clamp the flask at an angle of 45°, and cautiously add a few mL of a mixture of 8 mL of sulfuric acid and 10 mL of nitric acid. Warm gently until the reaction commences, allow the reaction to subside, and proceed as directed for *If the substance is a solid,* beginning with "add additional portions of the same acid mixture."

Procedure—Treat the *Test Preparation* and the *Standard Preparation* as follows: ~~Adjust~~

■Using a pH meter, adjust■2S (*USP27*) the solution to a pH between 3.0 and 4.0, ~~using short range pH indicator paper as external indicator,~~

■■2S (*USP27*) with ammonium hydroxide (a dilute ammonia solution may be used, if desired, as the specified range is approached), dilute with water to 40 mL, and mix.

To each tube add 2 mL of *pH 3.5 Acetate Buffer,* then add 1.2 mL of thioacetamide-glycerin base TS, dilute with water to 50 mL, mix, allow to stand for 2 minutes, and view downward over a white surface*: the color of the *Test Preparation* is not darker than that of the *Standard Preparation.*

In-Process Revision

Physical Tests and Determinations

BRIEFING

⟨**611**⟩ **Alcohol Determination,** *USP 26* page 2124. This general chapter is revised to incorporate two new Reference Standards for *Method II—Gas-Liquid Chromatographic Method*. The use of these Reference Standards will allow a more accurate determination and decrease the number of analytical manipulations. Minor editorial style changes have also been made.

(PA4: H. Pappa) RTS—39929-1

Change to read:

METHOD II—GAS-LIQUID CHROMATOGRAPHIC METHOD

Method II is to be used where specified in the individual monograph. For a discussion of the principles upon which it is based, see *Gas Chromatography* under *Chromatography* ⟨621⟩.

■**USP Reference Standards**—*USP Alcohol Determination—Acetonitrile RS. USP Alcohol Determination—Alcohol RS.*■2S (*USP27*)

Apparatus—Under typical conditions, use a gas chromatograph equipped with a flame-ionization detector and a 1.8-m × 4-mm (ID) glass column packed with 100- to 120-mesh chromatographic column packing No. S3, using nitrogen or helium as the carrier. Prior to use, condition the column overnight at 235° with a slow flow of carrier gas. The column is maintained at 120°, and the injection port and detector are maintained at 210°. Adjust the carrier flow and temperature so that acetonitrile, the internal standard, elutes in 5 to 10 minutes.

Solutions—

~~*Standard Solution*—Dilute 5.0 mL of dehydrated alcohol with water to 250 mL.~~

~~*Internal Standard Solution*—Dilute 5.0 mL of acetonitrile with water to 250 mL.~~

■■2S (*USP27*)

Test Stock Preparation—Dilute the specimen under examination stepwise with water to obtain a solution containing approximately 2% (v/v) of alcohol.

Test Preparation—Pipet ~~10 mL each of the *Test Solution* and the *Internal Standard Solution* into a 100-mL~~

■5 mL each of the *Test Stock Preparation* and the USP Alcohol Determination—Acetonitrile RS into a 50-mL■2S (*USP27*) volumetric flask, and dilute with water to volume.

Standard Preparation—Pipet ~~10 mL each of the *Standard Solution* and the *Internal Standard Solution* into a 100-mL~~

■5 mL each of the USP Alcohol Determination—Alcohol RS and the USP Alcohol Determination—Acetonitrile RS into a 50-mL■2S (*USP27*) volumetric flask, dilute with water to volume, and mix.

Procedure—Inject about 5 µL each of *Test Preparation* and *Standard Preparation,* in duplicate, into the gas chromatograph, record the chromatograms, and determine the peak response ratios. Calculate the percentage of alcohol (v/v) in the specimen under test according to the formula:

~~$2R_U D / R_S$~~,

■$CD(R_U / R_S)$,■2S (*USP27*)

in which

■C is the labeled concentration of USP Alcohol Determination—Alcohol RS;■2S (*USP27*) D is the dilution factor (the ratio of the volume of the *Test Stock Preparation* to the volume of the specimen taken); and R_U and R_S are the peak response ratios obtained for the *Test Preparation* and the *Standard Preparation,* respectively.

System Suitability Test—In a suitable chromatogram, the resolution factor, *R,* is not less than 2; the tailing factor of the alcohol peak is not greater than 1.5; and six replicate injections of the *Standard Preparation* show a relative standard deviation of not more than 2.0% in the ratio of the peak of alcohol to the peak of the internal standard.

BRIEFING

⟨**621**⟩ **Chromatography,** *USP 26* page 2126, page 3154 of the *Second Supplement,* and page 1210 of *PF* 29(4) [July–Aug. 2003]. It is proposed to add a new L designation for the column used in the *Assay* and in the *Related compounds* test in the monograph for *Clopidogrel Bisulfate,* which appears in this number of *PF.*

(HDQ: M. Marques) RTS—40149-1

Change to read:

CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE—Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

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Packings

L1—Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to 10 µm in diameter.

L2—Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to 50 µm in diameter.

L3—Porous silica particles, 5 to 10 µm in diameter.

L4—Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L5—Alumina of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L6—Strong cation-exchange packing–sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to 50 µm in diameter.

L7—Octylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L8—An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, 10 µm in diameter.

L9—10-µm irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10—Nitrile groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L11—Phenyl groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L12—A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to 50 µm in diameter.

L13—Trimethylsilane chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L14—Silica gel 10 µm in diameter having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating.

L15—Hexylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L16—Dimethylsilane chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L17—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to 11 µm in diameter.

L18—Amino and cyano groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L19—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about 9 µm in diameter.

L20—Dihydroxypropane groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L21—A rigid, spherical styrene-divinylbenzene copolymer, 5 to 10 µm in diameter.

L22—A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about 10 µm in size.

L23—An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about 10 µm in size.

L24—A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to 63 µm in diameter.[5]

L25—Packing having the capacity to separate compounds with a molecular weight range from 100–5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26—Butyl silane chemically bonded to totally porous silica particles, 5 to 10 µm in diameter.

L27—Porous silica particles, 30 to 50 µm in diameter.

L28—A multifunctional support, which consists of a high purity, 100 Å, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.

L29—Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, 5 µm in diameter with a pore volume of 80 Å.

L30—Ethyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L31—A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of 8.5-µm macroporous particles having a pore size of 2000 Å and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene.

L32—A chiral ligand-exchange packing–L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to 10 µm in diameter.

L33—Packing having the capacity to separate ■dextrans■1S (*USP26*) by molecular size over a range of 4,000 to ■500,000■1S (*USP26*) Da. It is spherical, silica-based, and processed to provide pH stability.■[6]■1S (*USP26*)

L34—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about 9 µm in diameter.

L35—A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of 150 Å.

L36—A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to 5-µm aminopropyl silica.

L37—Packing having the capacity to separate proteins by molecular size over a range of 2,000 to 40,000 Da. It is a polymethacrylate gel.

L38—A methacrylate-based size-exclusion packing for water-soluble samples.

L39—A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40—Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to 20 µm in diameter.

L41—Immobilized α_1-acid glycoprotein on spherical silica particles, 5 µm in diameter.

L42—Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, 5 µm in diameter.

L43—Pentafluorophenyl groups chemically bonded to silica particles

■by a propyl spacer,■1S (*USP27*)
5 to 10 µm in diameter.

L44—A multifunctional support, which consists of a high purity, 60 Å, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45—Beta cyclodextrin bonded to porous silica particles, 5 to 10 µm in diameter.

L46—Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, 10 µm in diameter.

L47—High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.[7]

L48—Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, 15 µm in diameter.

L49—A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to 10 µm in diameter.[8]

[5] Available as ~~Fractogel TSK HW 40F and distributed by Merck and Co.~~ ■YMC-Pack PVA-SIL manufactured by YMC Co., Ltd.■1S (*USP27*)

[6] Available as TSKgel G4000 SWXL from TosoHaas (www.tosohaas.com).

[7] Available as CarboPac MA1 and distributed by Dionex Corporation.

[8] Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.

In-Process Revision

L50—Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm in diameter, and a surface area not less than 350 m^2 per g. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene.[9]

▲L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to 10 µm in diameter.[10] ▲*USP26*

▲L52—A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.[11] ▲*USP26*

■L53—Weak cation-exchange resin consisting of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than 500 µEq/column. [12] ■1S (*USP26*)

■L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter. [13] ■2S (*USP26*)

■L~~53~~ ## (Alendronic Acid Tablets, PRP-X100)—An anion-exchange resin consisting of a rigid, spherical styrene-divinylbenzene copolymer with trimethylammonium groups at a loading of about 2 mEq per g, 3 to 20 µm in diameter.[a] ■1S (*USP27*)

■L~~54~~ ## (Maltose, Aminex HPX-87N)—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.[b] ■1S (*USP27*)

■L~~57~~ ## (Nevirapine, Supelcosil ABZ)—Spherical, porous silica gel, 3 or 5 µm in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about 6 µmoles per m^2.[c] ■1S (*USP27*)

■L~~58~~ ## (Albumin Human, TSKgel G3000 SW)—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa. It is spherical (10 µm), silica-based, and processed to provide hydrophilic characteristics and pH stability.[d] ■1S (*USP27*)

▲L~~59~~ ## (Clonidine, Zorbax SB-C3)—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.[e] ▲*USP27*

▲L~~60~~ ## Bethanecol Chloride, Bethanecol Chloride Tablets, IC-Pak C M/D)—A strong cation exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.[f] ▲*USP27*

■L~~61~~ ## (Lycopene, Lycopene Preparation, YMC 30)—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter. ■1S (*USP27*)

■L## (Clopidogrel Bisulfate, Ultron ES-OVM)—A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about 5 µm in diameter, with a pore size of 120 Å. ■2S (*USP27*)

Phases

G1—Dimethylpolysiloxane oil.
G2—Dimethylpolysiloxane gum.
G3—50% Phenyl-50% methylpolysiloxane.
G4—Diethylene glycol succinate polyester.
G5—3-Cyanopropylpolysiloxane.
G6—Trifluoropropylmethylpolysiloxane.
G7—50% 3-Cyanopropyl-50% phenylmethylsilicone.
G8—80% Bis(3-cyanopropyl)-20% 3-cyanopropylphenylpolysiloxane (percentages refer to molar substitution).
G9—Methylvinylpolysiloxane.
G10—Polyamide formed by reacting a C_{36} dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00:0.90:0.20.
G11—Bis(2-ethylhexyl) sebacate polyester.
G12—Phenyldiethanolamine succinate polyester.
G13—Sorbitol.
G14—Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15—Polyethylene glycol (av. mol. wt. of 3000 to 3700).

[9] Available as OmniPac PAX-500 and distributed by Dionex Corporation.

[10] Available as Chiralpak AD from Chiral Technologies, Inc., 730 Springdale Drive, P.O. Box 564, Exton, PA 19341.

[11] Available as TSK IC SW Cation from TosoHaas.

[12] Available as IonPac CS14 distributed by Dionex Corporation (www.dionex.com).

[13] Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).

[a] Available as PRP-X100 from Hamilton Company (www.hamiltoncompany.com).

[b] Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143), Group Headquarters, Bio-Rad Laboratories, 2000 Alfred Nobel Dr., Hercules, California 94547 (www.discover.bio-rad.com).

[c] Available as Supelcosil ABZ from Supelco. (www.sigma-aldrich.com/supelco)

[d] Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05103 and 05317, respectively). (www.tosohbiosep.com)

[e] Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)

[f] Available as IC-Pak C M/D from Waters Corp. (www.waters.com).

In-Process Revision

G16—Polyethylene glycol compound (av. mol. wt. about 15,000). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.

G17—75% Phenyl-25% methylpolysiloxane.

G18—Polyalkylene glycol.

G19—25% Phenyl-25% cyanopropyl-50% methylsilicone.

G20—Polyethylene glycol (av. mol. wt. of 380 to 420).

G21—Neopentyl glycol succinate.

G22—Bis(2-ethylhexyl) phthalate.

G23—Polyethylene glycol adipate.

G24—Diisodecyl phthalate.

G25—Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.

G26—25% 2-Cyanoethyl-75% methylpolysiloxane.

G27—5% Phenyl-95% methylpolysiloxane.

G28—25% Phenyl-75% methylpolysiloxane.

G29—3,3′-Thiodipropionitrile.

G30—Tetraethylene glycol dimethyl ether.

G31—Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30.

G32—20% Phenylmethyl-80% dimethylpolysiloxane.

G33—20% Carborane-80% methylsilicone.

G34—Diethylene glycol succinate polyester stabilized with phosphoric acid.

G35—A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.

G36—1% Vinyl-5% phenylmethylpolysiloxane.

G37—Polyimide.

G38—Phase G1 containing a small percentage of a tailing inhibitor.[14]

G39—Polyethylene glycol (av. mol. wt. about 1500).

G40—Ethylene glycol adipate.

G41—Phenylmethyldimethylsilicone (10% phenyl-substituted).

G42—35% phenyl-65% dimethylpolysiloxane (percentages refer to molar substitution).

G43—6% cyanopropylphenyl-94% dimethylpolysiloxane (percentages refer to molar substitution).

G44—2% low molecular weight petrolatum hydrocarbon grease and 1% solution of potassium hydroxide.

G45—Divinylbenzene-ethylene glycol-dimethylacrylate.

G46—14% Cyanopropylphenyl-86% methylpolysiloxane.

G47—Polyethylene glycol (av. mol. wt. of about 8000).

G48—Highly polar, partially cross-linked cyanopolysiloxane.

■G49—Proprietary derivatized phenyl groups on a polysiloxane backbone.[15] ■1S (*USP26*)

■G~~50~~ ## (Docosahexaenoic Acid)—Polyethylene glycol, cross-linked (av. mol. wt. of more than 20,000).[g] ■1S (*USP27*)

Supports

[NOTE—Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.]

S1A—Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with Na_2CO_3 flux and calcining above 900°. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane[16] to mask surface silanol groups.

S1AB—The siliceous earth as described above is both acid- and base-washed.[16]

S1C—A support prepared from crushed firebrick and calcined or burned with a clay binder above 900° with subsequent acid-wash. It may be silanized.

S1NS—The siliceous earth is untreated.

S2—Styrene-divinylbenzene copolymer having a nominal surface area of less than 50 m^2 per g and an average pore diameter of 0.3 to 0.4 μm.

S3—Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to 600 m^2 per g and an average pore diameter of 0.0075 μm.

S4—Styrene-divinylbenzene copolymer with aromatic –O and –N groups, having a nominal surface area of 400 to 600 m^2 per g and an average pore diameter of 0.0076 μm.

S5—40- to 60-mesh, high-molecular weight tetrafluorethylene polymer.

S6—Styrene-divinylbenzene copolymer having a nominal surface area of 250 to 350 m^2 per g and an average pore diameter of 0.0091 μm.

S7—Graphitized carbon having a nominal surface area of 12 m^2 per g.

S8—Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9—A porous polymer based on 2,6-diphenyl-*p*-phenylene oxide.

S10—A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11—Graphitized carbon having a nominal surface area of 100 m^2 per g modified with small amounts of petrolatum and polyethylene glycol compound.[17]

S12—Graphitized carbon having a nominal surface area of 100 m^2 per g.

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[14] A suitable grade is available commercially as "SP2100/0.1% Carbowax 1500" from Supelco, Inc., Supelco Park, Bellefonte, PA 16823.

[15] A suitable grade is available commercially as "Optima Delta 3" from Machery-Nagel, Inc., 215 River Vale Road, River Vale, NJ 07675.

[g] A suitable grade is available commercially as Famewax from Restek.

[16] Unless otherwise specified in the individual monograph, silanized support is intended.

[17] Commercially available as SP1500 on Carbopack B from Supelco.

BRIEFING

⟨**921**⟩ **Water Determination,** *USP 26* page 2230. On the basis of comments received, it is proposed to revise the *Apparatus* section under *Method Ia* to reflect current technology. Also, it is proposed to revise the *Principle* section under *Method 1c* (*Coulometric Titration*).

(PA4: H. Pappa) RTS—40179-1

Change to read:

METHOD I (TITRIMETRIC)

Determine the water by *Method Ia,* unless otherwise specified in the individual monograph.

Method Ia (Direct Titration)

Principle—The titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulfur dioxide and iodine in the presence of a buffer that reacts with hydrogen ions.

In the original titrimetric solution, known as Karl Fischer Reagent, the sulfur dioxide and iodine are dissolved in pyridine and methanol. The test specimen may be titrated with the *Reagent* directly, or the analysis may be carried out by a residual titration procedure. The stoichiometry of the reaction is not exact, and the reproducibility of a determination depends upon such factors as the relative concentrations of the *Reagent* ingredients, the nature of the inert solvent used to dissolve the test specimen, and the technique used in the particular determination. Therefore, an empirically standardized technique is used in order to achieve the desired accuracy. Precision in the method is governed largely by the extent to which atmospheric moisture is excluded from the system. The titration of water is usually carried out with the use of anhydrous methanol as the solvent for the test specimen; however, other suitable solvents may be used for special or unusual test specimens.

Apparatus—Any apparatus may be used that provides for adequate exclusion of atmospheric moisture and determination of the endpoint. In the case of a colorless solution that is titrated directly, the endpoint may be observed visually as a change in color from canary yellow to amber. The reverse is observed in the case of a test specimen that is titrated residually. More commonly, however, the endpoint is determined electrometrically with an apparatus employing a simple electrical circuit that serves to impress about 200 mV of applied potential between a pair of platinum electrodes ~~(about 5 mm² in area and about 2.5 cm apart)~~

■■2S (*USP27*)
immersed in the solution to be titrated. At the endpoint of the titration a slight excess of the reagent increases the flow of current to between 50 and 150 microamperes for 30 seconds to 30 minutes, depending upon the solution being titrated. The time is shortest for substances that dissolve in the reagent. With some automatic titrators, the abrupt change in current or potential at the endpoint serves to close a solenoid-operated valve that controls the buret delivering the titrant. Commercially available apparatus generally comprises a closed system consisting of one or two automatic burets and a tightly covered titration vessel fitted with the necessary electrodes and a magnetic stirrer. The air in the system is kept dry with a suitable desiccant, and the titration vessel may be purged by means of a stream of dry nitrogen or current of dry air.

Reagent—Prepare the Karl Fischer Reagent as follows. Add 125 g of iodine to a solution containing 670 mL of methanol and 170 mL of pyridine, and cool. Place 100 mL of pyridine in a 250-mL graduated cylinder, and, keeping the pyridine cold in an ice bath, pass in dry sulfur dioxide until the volume reaches 200 mL. Slowly add this solution, with shaking, to the cooled iodine mixture. Shake to dissolve the iodine, transfer the solution to the apparatus, and allow the solution to stand overnight before standardizing. One mL of this solution when freshly prepared is equivalent to approximately 5 mg of water, but it deteriorates gradually; therefore, standardize it within 1 hour before use, or daily if in continuous use. Protect from light while in use. Store any bulk stock of the reagent in a suitably sealed, glass-stoppered container, fully protected from light, and under refrigeration.

A commercially available, stabilized solution of Karl Fischer type reagent may be used. Commercially available reagents containing solvents or bases other than pyridine or alcohols other than methanol may be used also. These may be single solutions or reagents formed in situ by combining the components of the reagents present in two discrete solutions. The diluted *Reagent* called for in some monographs should be diluted as directed by the manufacturer. Either methanol or other suitable solvent, such as ethylene glycol monomethyl ether, may be used as the diluent.

Test Preparation—Unless otherwise specified in the individual monograph, use an accurately weighed or measured amount of the specimen under test estimated to contain 10 to 250 mg of water.

Where the specimen under test is an aerosol with propellant, store it in a freezer for not less than 2 hours, open the container, and test 10.0 mL of the well-mixed specimen. In titrating the specimen, determine the endpoint at a temperature of 10° or higher.

Where the specimen under test is capsules, use a portion of the mixed contents of not less than 4 capsules.

Where the specimen under test is tablets, use powder from not less than 4 tablets ground to a fine powder in an atmosphere of temperature and relative humidity known not to influence the results.

Where the monograph specifies that the specimen under test is hygroscopic, use a dry syringe to inject an appropriate volume of methanol, or other suitable solvent, accurately measured, into a tared container, and shake to dissolve the specimen. Using the same syringe, remove the solution from the container and transfer it to a titration vessel prepared as directed for *Procedure.* Repeat the procedure with a second portion of methanol, or other suitable solvent, accurately measured, add this washing to the titration vessel, and immediately titrate. Determine the water content, in mg, of a portion of solvent of the same total volume as that used to dissolve the specimen and to wash the container and syringe, as directed for *Standardization of Water Solution for Residual Titrations,* and subtract this value from the water content, in mg, obtained in the titration of the specimen under test. Dry the container and its closure at 100° for 3 hours, allow to cool in a desiccator, and weigh. Determine the weight of specimen tested from the difference in weight from the initial weight of the container.

Standardization of the Reagent—Place enough methanol or other suitable solvent in the titration vessel to cover the electrodes, and add sufficient *Reagent* to give the characteristic endpoint color, or 100 ± 50 microamperes of direct current at about 200 mV of applied potential.

For determination of trace amounts of water (less than 1%), sodium tartrate may be used as a convenient water reference substance. Quickly add 150 to 350 mg of sodium tartrate ($C_4H_4Na_2O_6 \cdot 2H_2O$), accurately weighed by difference, and titrate to the endpoint. The water equivalence factor *F,* in mg of water per mL of reagent, is given by the formula:

$$2(18.02/230.08)(W/V),$$

in which 18.02 and 230.08 are the molecular weights of water and sodium tartrate dihydrate, respectively; *W* is the weight, in mg, of sodium tartrate dihydrate; and *V* is the volume, in mL, of the *Reagent* consumed in the second titration.

In-Process Revision

For the precise determination of significant amounts of water (1% or more), use *Purified Water* as the reference substance. Quickly add between 25 and 250 mg of water, accurately weighed by difference, from a weighing pipet or from a precalibrated syringe or micropipet, the amount taken being governed by the reagent strength and the buret size, as referred to under *Volumetric Apparatus* ⟨31⟩. Titrate to the endpoint. Calculate the water equivalence factor, *F,* in mg of water per mL of reagent, by the formula:

$$W/V,$$

in which W is the weight, in mg, of the water; and V is the volume, in mL, of the reagent required.

Procedure—Unless otherwise specified, transfer 35 to 40 mL of methanol or other suitable solvent to the titration vessel, and titrate with the *Reagent* to the electrometric or visual endpoint to consume any moisture that may be present. (Disregard the volume consumed, since it does not enter into the calculations.) Quickly add the *Test Preparation,* mix, and again titrate with the *Reagent* to the electrometric or visual endpoint. Calculate the water content of the specimen, in mg, taken by the formula:

$$SF,$$

in which S is the volume, in mL, of the *Reagent* consumed in the second titration; and F is the water equivalence factor of the *Reagent.*

Method Ib (Residual Titration)

Principle—See the information given in the section *Principle* under *Method Ia.* In the residual titration, excess *Reagent* is added to the test specimen, sufficient time is allowed for the reaction to reach completion, and the unconsumed *Reagent* is titrated with a standard solution of water in a solvent such as methanol. The residual titration procedure is applicable generally and avoids the difficulties that may be encountered in the direct titration of substances from which the bound water is released slowly.

Apparatus, Reagent, and Test Preparation—Use *Method Ia.*

Standardization of Water Solution for Residual Titration—Prepare a *Water Solution* by diluting 2 mL of water with methanol or other suitable solvent to 1000 mL. Standardize this solution by titrating 25.0 mL with the *Reagent,* previously standardized as directed under *Standardization of the Reagent.* Calculate the water content, in mg per mL, of the *Water Solution* taken by the formula:

$$V'F/25,$$

in which V' is the volume of the *Reagent* consumed, and F is the water equivalence factor of the *Reagent.* Determine the water content of the *Water Solution* weekly, and standardize the *Reagent* against it periodically as needed.

Procedure—Where the individual monograph specifies that the water content is to be determined by *Method Ib,* transfer 35 to 40 mL of methanol or other suitable solvent to the titration vessel, and titrate with the *Reagent* to the electrometric or visual endpoint. Quickly add the *Test Preparation,* mix, and add an accurately measured excess of the *Reagent.* Allow sufficient time for the reaction to reach completion, and titrate the unconsumed *Reagent* with standardized *Water Solution* to the electrometric or visual endpoint. Calculate the water content of the specimen, in mg, taken by the formula:

$$F(X' - XR),$$

in which F is the water equivalence factor of the *Reagent; X'* is the volume, in mL, of the *Reagent* added after introduction of the specimen; X is the volume, in mL, of standardized *Water Solution* required to neutralize the unconsumed *Reagent;* and R is the ratio, $V'/25$ (mL *Reagent*/mL *Water Solution*), determined from the *Standardization of Water Solution for Residual Titration.*

Method Ic (Coulometric Titration)

Principle—The Karl Fischer reaction is used in the coulometric determination of water. Iodine, however, is not added in the form of a volumetric solution but is produced in an iodide-containing solution by anodic oxidation. The reaction cell usually consists of a large anode compartment and a small cathode compartment that are separated by a diaphragm. Other suitable types of reaction cells (e.g., without diaphragms) may also be used. Each compartment has a platinum electrode that conducts current through the cell. Iodine, which is produced at the anode electrode, immediately reacts with water present in the compartment. When all the water has been consumed, an excess of iodine occurs, which usually is detected electrometrically, thus indicating the endpoint. Moisture is eliminated from the system by pre-electrolysis. Changing the Karl Fischer solution after each determination is not necessary since individual determinations can be carried out in succession in the same reagent solution. A requirement for this method is that each component of the test specimen is compatible with the other components, and no side reactions take place. Samples are usually transferred into the vessel as solutions by means of injection through a septum. Gases can be introduced into the cell by means of a suitable gas inlet tube. Precision in the method is predominantly governed by the extent to which atmospheric moisture is excluded from the system; thus, the introduction of solids into the cell is not recommended, unless elaborate precautions are taken, such as working in a glove-box in an atmosphere of dry inert gas. Control of the system may be monitored by measuring the amount of baseline drift. This method is particularly suited to chemically inert substances like hydrocarbons, alcohols, and ethers. In comparison with the volumetric Karl Fischer titration, coulometry is a micro-method. ~~The method utilizes extremely small amounts of current and is used to determine water content in the range of 100% to 0.0001%.~~

■■2S (*USP27*)

Apparatus—Any commercially available apparatus consisting of an absolutely tight system fitted with the necessary electrodes and a magnetic stirrer is appropriate. The instrument's microprocessor controls the analytical procedure and displays the results. Calibration of the instrument is not necessary, as the current consumed can be measured absolutely.

Reagent—See *Reagent* under *Method Ia.*

Test Preparation—Where the specimen is a soluble solid, dissolve an appropriate quantity, accurately weighed, in anhydrous methanol or other suitable solvents. Liquids may be used as such or as accurately prepared solutions in appropriate anhydrous solvents.

Where the specimen is an insoluble solid, the water may be extracted using a suitable anhydrous solvent from which an appropriate quantity, accurately weighed, may be injected into the anolyte solution. Alternatively an evaporation technique may be used in which water is released and evaporated by heating the specimen in a tube in a stream of dry inert gas, this gas being then passed into the cell.

Procedure—Using a dry syringe, quickly inject the *Test Preparation,* accurately measured and estimated to contain 0.5 to 5 mg of water, or as recommended by the instrument manufacturer into the anolyte, mix, and perform the coulometric titration to the electrometric endpoint. Read the water content of the *Test Preparation* directly from the instrument's display, and calculate the percentage that is present in the substance. Perform a blank determination, and make any necessary corrections.

In-Process Revision

GENERAL CHAPTERS

General Information

BRIEFING

⟨1079⟩ Good Storage and Shipping Practices. This new proposed general information chapter is intended to provide guidance to manufacturers, repackagers, distributors, shippers, and pharmacists on practices designed to maintain the integrity of pharmaceuticals during storage and shipment. The chapter was drafted based in part on storage and shipping portions of the text of the formerly proposed general chapter *Packaging, Storage, and Distribution of Pharmacopeial Articles* ⟨1141⟩, as published on page 493 of *PF* 26(2) [Mar.–Apr. 2000].

References are made in the text to the proposed general chapter *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩, published on page 476 of *PF* 28(2) [Mar.–Apr. 2002] and to *Pharmaceutical Stability* ⟨1150⟩, a renamed section of *Pharmaceutical Dosage Forms* ⟨1151⟩, a general information chapter appearing elsewhere in this number of *PF*.

Additional information from the previously proposed chapter ⟨1141⟩ related to packaging can be found in the new proposed general chapter *Good Packaging Practices* ⟨1177⟩, also appearing in this number of *PF*. Comments should be addressed to Dr. Claudia Okeke, USP Information and Standards Development.

(PSD: C. Okeke) RTS—40189-01

Add the following:

■⟨1079⟩ GOOD STORAGE AND SHIPPING PRACTICES

This general chapter is intended to provide general guidance concerning storing, distributing, and shipping of Pharmacopeial preparations. It describes procedures that should be considered to ensure that the standards for proper storage environments for individual articles are maintained. Approaches in this chapter are designed to ensure that the article's integrity is maintained until it reaches the user. It does not change any applicable requirements under good manufacturing practices, state laws governing pharmacies, the *USP General Notices and Requirements* or monographs, or provisions under approved labeling.

The section *Preservation, Packaging, Storage, and Labeling* under the *General Notices* provides definitions for storage conditions. All equipment used for recording, monitoring, and maintaining these temperatures and humidity conditions should be calibrated on a regular basis. This calibration should be traceable to national or international standards (see *Monitoring Devices—Time, Temperature, and Humidity* ⟨1118⟩).

A Pharmacopeial preparation may follow several potential routes from the original manufacturer to the patient. *Figure 1* documents these routes and the risks to the associated product. These risks include exposure to temperature excursions, humidity, light, and oxygen. For a discussion of climates, stability, and mean kinetic temperature, see *Pharmaceutical Stability* ⟨1150⟩. Temperature- or humidity-sensitive articles are to be handled in accordance with guidelines provided in the *General Notices*.

PACKAGING AND STORAGE STATEMENT IN MONOGRAPHS

Most articles have storage conditions identified by their labeling. Otherwise, it is expected that the conditions for storing the article are specified in the monograph according to definitions provided under *Storage Temperature* in the *Preservation, Packaging, Storage, and Labeling* section of the *General Notices*.

In cases where additional information on the article is desired, the packaging and storage information can be explained further in the *Packaging and storage* or the *Labeling* section of the monograph with specific handling instructions for the article.

In-Process Revision

STORAGE IN WAREHOUSES, PHARMACIES, TRUCKS, SHIPPING DOCKS, AND OTHER LOCATIONS

Pharmacopeial articles are to be stored in locations that adhere to conditions established by the manufacturer. Where conditions are not established or available, use storage conditions described in the *General Notices* or the applicable monograph.

Warehouses

Observation of the temperature variations in a warehouse should be made over a period of time to establish a meaningful temperature profile, including the temperature variations and conditions in the different parts of the warehouse. Such observations provide data and information as to where various products should and should not be stored.

ESTABLISHING TEMPERATURE PROFILES

Temperature profiles can be achieved by using a suitable number of thermometers or other temperature recording instruments or monitoring devices and placing them throughout the warehouse in divided sections, and recording the maximum and minimum temperatures achieved during a 24-hour period for a total of three consecutive 24-hour periods. With regard to temperature profiling, the following factors should be considered during the process: the size of the warehouse and conditions that give rise to predisposition to extreme temperatures such as location of space heaters, sun-facing walls, low ceilings or roofs, and regional location of the warehouse.

Temperature profiling on warehouses already in use can be done at known high external temperature times (e.g., for a period of over three hours in the daytime when ambient air temperatures are higher than 25° and when temperatures are known to be less than 15°). This exercise should be conducted in the summer and winter seasons, as these are times of extreme temperatures.

A mean kinetic temperature (MKT) of the temperature profile should be obtained and recorded for any separate areas within the warehouse; see general chapter *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩ for samples of MKT calculations. The report from the profile should provide recommendations for the use of each area and identification of any areas that are found unsuitable for storage of Pharmacopeial articles.

CONTROLLED ROOM TEMPERATURE

The *General Notices* provide a definition for controlled room temperature. A temperature profiling study should demonstrate suitability for storing Pharmacopeial articles in areas determined to be "room" or "controlled room" temperature. A suitable number of temperature and humidity recording instruments should be installed to record temperatures and provide temperature and humidity profiles. Temperature recording should be conducted to meet the recommendations for establishing mean kinetic temperature and to comply with the warehouse's written procedures. These written procedures should have a reporting mechanism in place whereby a management tree is informed in the event that predefined high or low temperatures or humidity limits have been exceeded.

Records can be reviewed as determined by the management system in accordance with established guidelines. Suitable training should be provided to persons who record temperatures, and proper quality accountability and tracking systems should be maintained.

STORAGE AT "COOL," "COLD," "REFRIGERATOR," AND "FREEZING" CONDITIONS

The *General Notices* provide definitions for ''cool,'' "cold," "refrigerator," and "freezer" temperatures. A temperature profiling study can be used to establish suitable areas for storing Pharmacopeial articles designated to be stored under these conditions. Equipment used for storing Pharmacopeial articles at these low temperatures should be validated according to written procedures provided by the management system. Recording devices can be installed within the equipment and used to enable both air and product temperatures to be recorded at regular intervals. The number and location of monitoring devices should be determined based on the result of the temperature profile. Temperature records should be examined at least once every 24 hours or as provided in the equipment protocol. Humidity-monitoring devices should be used in cases where the Pharmacopeial article is humidity-sensitive or labeled to avoid moisture. In this case, proper records must be maintained of the humidity in the area where the Pharmacopeial article is stored. Additionally, there can be installed temperature-monitoring, and where necessary, humidity-monitoring equipment that has the capability of alerting personnel in the event that temperature or humidity control is compromised. There should be protocols in place to address procedures for responding to failed temperature and humidity ranges both for normal working hours and outside normal working hours. Temperature and humidity should be reviewed at the times designated by the established protocol. The calibration and functioning of all temperature and humidity monitoring devices, including alarms and other associated equipment, should be checked on an annual or semiannual basis. Regular maintenance protocols should be in place for refrigeration equipment. There should be written agreements in place for all maintenance and evaluation procedures, and this may include an emergency situation protocol.

PERSONNEL TRAINING

Suitable training should be provided for personnel who handle Pharmacopeial articles with special storage temperature requirements. Personnel should know how to monitor temperatures and how to react to situations where adverse temperatures are identified. There should be written procedures in place such that the adverse temperatures are recorded and a report provided to the parties designated in the protocol.

VALIDATION OF "COLD" EQUIPMENT OR STORES

Only climate control equipment for which a contractor has provided documentation to assure its suitability for temperature and humidity requirements should be considered for use in cold storage. Validation procedures should be independently conducted on equipment in cold stores regularly to guarantee its suitability and proper functioning. The validation should demonstrate the temperature profile throughout the proposed equipment for both air and product temperatures both when empty and when loaded. The validation should also demonstrate the time taken for temperatures to exceed the maximum temperature in the event of a power failure. Validation should consider thermal fluctuations that occur during stock replenishment and order removal. The results of the validation should demonstrate

the ability of the equipment to maintain the required temperature range in all areas, defining any zones which should not be used for storage such as those areas in close proximity to cooling coils, cold air streams from equipment ventilation, or doors. The variability of the system should also be characterized by using the relative standard deviation. Thermal monitoring should establish that the system is rugged in that its temperature profile is consistent and reliable.

DISTRIBUTION AND SHIPMENT OF PHARMACOPEIAL ARTICLES

As indicated in *Figure 1*, a drug can take a variety of paths from the manufacturer to the patient. In the simplest form of the distribution system, the manufacturer ships directly to the customer, such as a doctor's office, clinic, or hospital. However, more often, the article leaves the manufacturer's chain of control and enters a complex system of handoffs that involve the distribution chain to the patient.

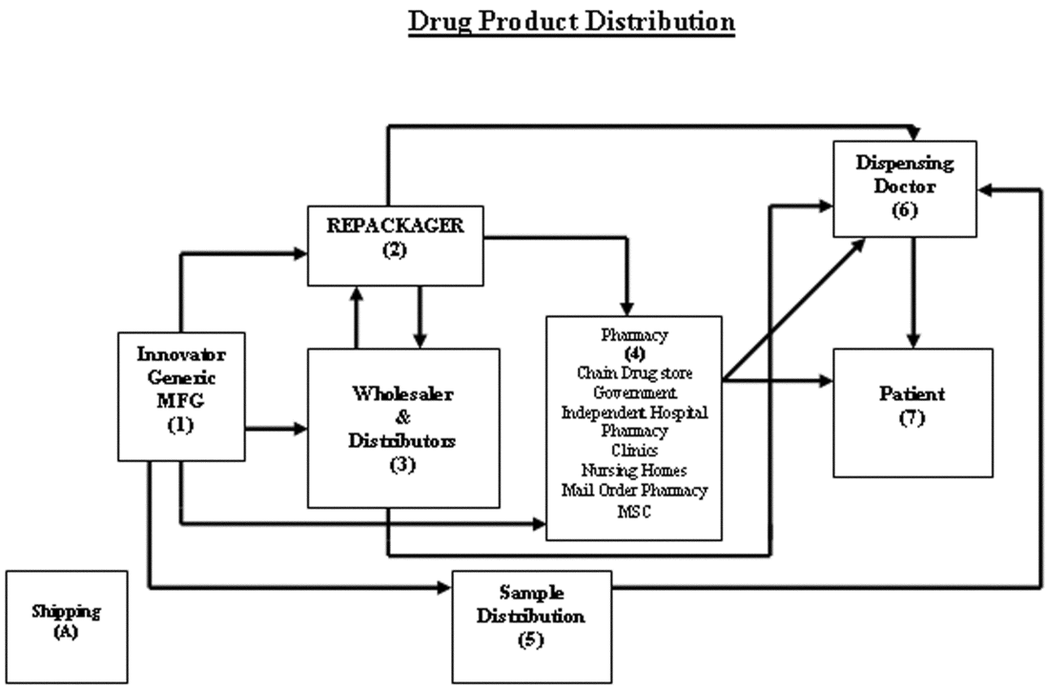

Figure 1. Drug product distribution.

Shippers and distributors are to follow the proper storage and shipping requirements as indicated by the manufacturer. For particular cases, such as shipment of vaccines or other special care products, manufacturers may require special shipping and storage conditions generally referred to as ''cold chain management''. For example, manufacturers may attach temperature-monitoring devices and/or ship under specified controlled conditions to ensure that the desired temperature is maintained during distribution. Validated, available temperature- and/or humidity-monitoring technol-

ogies can be used to monitor the overall environmental effect on compendial articles during shipment and distribution. In these cases, the shipping conditions of the package are recorded. In general, extreme temperature conditions (i.e., excessive heat, freezing) should be avoided.

Most products are sufficiently robust to withstand distribution with minimal protection from routine, well-understood physical and environmental hazards. Several standard test methods are available for evaluating package performance factors under well-documented shock, vibration, and other transit elements. The American Society for Testing and Materials document, "Standard Practice for Performance Testing of Shipping Containers and Systems" (ASTM D4169-98), and the International Safe Transit Association's (ISTA) specifications have similar methods for evaluation of shipping performance for various types of transit modes such as less-than-truckload (LTL), small package, rail car, air freight, etc. From the manufacturer's perspective, these tests are very useful in evaluating the product and package durability and fragility. The tests are usually performed on shipping carton quantities of a specific stock keeping unit (SKU) as an unbroken whole. Fragility problems can be corrected with package modifications. Some such modifications include placing cotton or rayon coilers in bottles or placing top and bottom pads in the shipping case to reduce package breakage. Not all protective packaging elements follow the SKU through the system.

Basic packaging principles are observed when separating the contents of the manufacturer's shipping container or pallet load into smaller quantities or when shipping mixed product loads. For example, glass containers are wrapped in a bubble wrap or other shock-absorbent material, and the void spaces are filled with dunnage (e.g., foam "peanuts," shredded or tightly crumpled paper, bubble wrap) to protect the contents from shifting and drop impact. Large-volume liquid containers may be bagged in plastic and kept isolated to prevent leakage to or damage of adjacent packages. "Skin packaging," a term describing a heat-shrink film that anchors the load to fiberboard and prevents load shift, can be an excellent method of protecting some products, but it may be inappropriate for heat-sensitive goods. The shipping carton should have correct Edge Crush Test (ECT) characteristics for freight being shipped according to Item 222 of the National Motor Freight Classification and Rule 41 of the Uniform Freight Classification.

Distribution systems chosen to deliver pharmaceutical products from the manufacturer to the consumer should take into account basic operational parameters, including timeliness and accountability. The manufacturer's FDA-approved storage conditions, printed in the labeling of the product, should be observed carefully at each destination of the distribution chain (see *Figure 1*). Items requiring special handling conditions will have those conditions clearly indicated in the labeling for the product. The Prescription Drug Marketing Act of 1987 and the ensuing regulations in 21 CFR Part 203, Prescription Drug Marketing, and Part 205, Guidelines for State Licensing of Wholesale Prescription Drug Distributors, provide the necessary regulations and guidance for several legs of the distribution chain for the prescription drug. The manufacturers and distributors should work together to establish proper distribution and product handling requirements for the purpose of ensuring appropriate product maintenance in transit. Pharmacists and physicians should educate patients regarding proper storage of products to ensure product integrity at the patient level.

Information that may be considered in determining the ability of pharmaceutical articles to maintain their Pharmacopeial requirements of identity, strength, quality, and purity through the distribution channel may include, but is not limited to:

- ICH stability studies,
- Temperature cycling studies,
- Stability shipping studies,
- Ongoing regulatory stability commitment studies,
- Market experience portfolio (i.e., product complaint files, historical product performance data, product development data), and
- Product labeling commitments.

Shipping of temperature-sensitive articles requiring thermally controlled packaging presents a special challenge. Unlike shock, vibration, and other physical hazards, thermal hazards tend to be unique to a given system. Except for temperature-controlled trucks, the distribution environment is widely variable and depends upon a range of factors. These factors include points of origin and destination, article and container sensitivities to cold, accidental freezing or heat, transit mode (e.g., air, truck, combination), time, weather or season, and carrier type (e.g., small package carrier or integrator, freight forwarder, U.S. Postal Service).

The shippers should know and understand the cold chain systems they use and design the protective package accordingly. Storage temperature ranges may not be indicative of the allowable tolerances during shipping. Articles labeled for special storage conditions (between 2° and 8°) vary widely in their tolerance of short-term exposure to heat and cold. Some, such as soft gelatin capsules and suppositories, carry specific upper limits on both shipping containers and SKUs. A temperature cycling study intended to identify those articles affected by multiple, short-term excursions beyond the storage temperature limits should be performed. These data provide wholesalers and distributors with clearer identification of those drug products that may require special handling during particular climate conditions.

Two commonly used types of refrigerant are dry ice (frozen carbon dioxide gas) and wet ice (frozen water), which appears as crushed ice or in various refrigerant packs containing water mixtures with specific freezing points. Phase-change materials are also available for specialized needs. Refrigerant packs should have the correct freezing point and be cooled to the proper surface temperature prior to use. Articles harmed by accidental freezing may require a barrier between the refrigerant and the product or some other special packaging.

Insulating materials commonly available include foil laminates, bubble pack, corrugated, fabricated, and molded expanded polystyrene (EPS) cartons, and fabricated or molded urethane foam cartons, with or without additional interior components. Recognized standard test methods for evaluating insulated containers are currently limited to ASTM D3103-92, "Standard Test Method for Thermal Insulation Quality of Packages" and a method under development by ISTA. Neither one fully addresses all of the issues involved, but both include useful information on testing procedures. The tests should be modified based on the specific system adopted by the shipper. The manufacturer may be able to supply helpful data on specific articles and their requirements.

Certain classes of Pharmacopeial articles may require special handling. Such articles include products classified as Dangerous Goods under the Department of Transportation (DOT), state, local, or carrier rules; or products classified as controlled substances by the Drug Enforcement Administration (DEA) or by individual states.

Receipt of Pharmacopeial Articles

Upon arrival of Pharmacopeial articles to warehouse loading docks, premises, and other arrival areas, the Pharmacopeial articles are to be transferred to their manufacturer-

designated storage environment within two hours of receipt. Limitation of the time spent in the uncontrolled environments of the loading dock is important to ensuring that the integrity of the preparation is maintained. This is particularly important for temperature-sensitive items.

The delivery document should be reviewed at receiving sites to ensure that the Pharmacopeial articles have not been subjected to any delays during shipment that could result in the article having been exposed to extremes of temperature, and that articles have not been exposed to extreme or undesirable conditions during shipment.

The receiving personnel should inspect and review the appropriate documents and verify that the container closure system used for storage, shipment, and distribution of the Pharmacopeial preparations meets the qualifications of protecting the articles from adverse storage conditions specific for the preparation such as solvent/gas permeation, light transmittance, moisture permeation, or microbial contamination as available from stability testing or in the applicable monograph(s). In addition, the receiving personnel should ensure that the ruggedness requirements in shipment have been met.

For Pharmacopeial articles requiring extreme caution, special handling, or refrigerator temperature storage conditions, those who supply the articles (e.g., wholesalers and manufacturers) and delivery contractors should provide documented evidence to show that the required temperature range has been maintained during transportation.

In the event that a deviation from the required temperature range has been observed during shipment of an article requiring such a shipping condition, the supplier or delivery contractors should document the temperature and the length of time the compendial article was not within the designated storage temperature. The pharmaceutical manufacturer may be contacted to determine the significance of unusual variances.

Distribution or Shipping Vehicles

Vehicles used for shipping or distribution of Pharmacopeial articles designated for storage at controlled room temperature should be suitably equipped to ensure that the temperature excursions encountered are within those allowed under the definition of controlled room temperature. Steps should be taken so that extremes of temperature, whether above or below the specified temperatures, should not be encountered during delivery procedures.

Vehicle Validation

Suitable monitoring devices as determined by the manufacturer and vehicle supplier should be placed in different areas of the truck to establish a temperature profile of the truck during a hot summer day and a cold winter day, and during a normal or typical day over a 24-hour period. The derived temperature of the different parts of the truck may be used to determine the location where Pharmacopeial articles are stored appropriately during shipping (see *Monitoring Devices—Time, Temperature and Humidity* ⟨1118⟩).

Pharmaceutical Delivery Staff

As part of the contractual agreement between the delivery contractors and the manufacturers, the delivery staff should receive appropriate training in order to ensure that they are aware of the correct procedures to follow in ensuring that products are maintained at the correct temperature. There may be written procedures that should be documented. In addition, the transportation personnel should have proper

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knowledge of the temperature profile of the vehicle to enable proper placement of the Pharmacopeial articles in the vehicle.

Pharmacopeial articles requiring special handling (e.g., refrigeration) or environmentally sensitive preparations should be transported in a suitably equipped vehicle to ensure that the articles are maintained at the correct temperature during distribution, shipping, and delivery up to the point of receipt. Special arrangements should be made to ensure that the attention of receiving personnel, pharmacists, or other appropriate customers is drawn to the fact that the package includes articles that have special storage and handling specifications so that the article is transferred immediately to the appropriate storage location. The manufacturer, shipper, or delivery agency should provide appropriate evidence to show that the required temperature has been maintained throughout shipment and distribution.

SHIPMENT FROM MANUFACTURER TO WHOLESALER

Wholesaler

The wholesaler receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment, as directed by the manufacturer, within two hours of receipt.

The wholesaler should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution which could result in products being exposed to extreme temperatures (see also the previous section, *Pharmaceutical Delivery Staff,* for staff expectations).

The vehicles used for shipping of Pharmacopeial articles to the wholesaler, especially products requiring storage at "low" temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt. The receiving wholesaler staff should be informed appropriately so that the articles are transferred to appropriate storage locations without delays.

The vehicles used for shipping of Pharmacopeial articles requiring storage at "room" or "controlled room" temperatures should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, not occur during delivery procedures. Warehouse staff may receive appropriate training in order to ensure that the correct procedures are followed to maintain required temperature conditions (see *Pharmaceutical Delivery Staff*). Where necessary, a monitoring device for temperature and/or humidity should be used during shipping and distribution.

Compromised Temperature Conditions

A procedure should be in place in the warehouse to define the action that should be taken in the event of deviation from required storage conditions. There should be maintenance of suitable records to explain the reason for deviation and the resulting action that is taken.

The product in question should then be placed in a quarantine status. Advice on the suitability of the product for use should be sought from the manufacturer or supplier of the product. The manufacturer's response should be documented prior to the issuing of the product to the customer, if that product is to be issued to the customer.

SHIPMENT FROM MANUFACTURER OR WHOLESALER TO PHARMACY

Pharmacy

The pharmacy receiving the pharmaceutical articles should ensure that on arrival, the pharmaceutical articles are transferred to the correct environment, as directed by the manufacturer, within two hours of receipt.

The pharmacy personnel should examine the delivery documentation to ensure that the products have not been subjected to any delays during shipping and distribution which could result in products being exposed to extreme temperatures (see also the section, *Pharmaceutical Delivery Staff,* for staff expectations).

The vehicles used for shipping of Pharmacopeial articles to the pharmacy, especially products requiring storage at "low" temperatures, should be suitably equipped to ensure that products are maintained at the correct temperature during shipping and distribution and up to the point of receipt. Receiving pharmacy staff should be informed appropriately so that the articles are transferred to appropriate storage without delays.

The vehicles used for shipping of Pharmacopeial articles requiring storage at "room" or "controlled room" temperatures should be suitably equipped to ensure that extremes of temperature, either above or below the specified temperature, do not occur during delivery procedures. Pharmacy staff may receive appropriate training in order to ensure that the correct procedures are followed to maintain required temperature conditions (see *Pharmaceutical Delivery Staff*). Where necessary, a monitoring device for temperature and/or humidity may be used during shipping and distribution.

Compromised Temperature Conditions

The pharmacy should maintain appropriate procedures to define action that should be taken in the event of deviation from the required storage conditions. There should be maintenance of suitable records to explain the reason for deviation and the resulting action taken (including whether the product is issued to the patient or customer). Advice on the suitability of the product for use as an acceptable drug article should be sought from the manufacturer or supplier of the product.

SHIPMENT FROM PHARMACY TO PATIENT OR CUSTOMER

The pharmacy should provide an appropriate label on the package sent through air or surface routes so the deliverer does not place the package in a mailbox exposed to extremes in temperature. In the event that no one is available to receive the package, the deliverer should return the package to the post office or service office and store it in a "cool" area until the patient can receive the medication. In the event that the package has not been delivered for more than two days, the package may be returned to the pharmacy. For temperature sensitive articles, it is important that proper arrangements be put in place to protect the drug from exposure to high temperatures, or in some cases, from freezing conditions. Such arrangements may include:

- Insulating packaging, or packaging with coolant included;
- Overnight shipping; and
- Pre-arranged pick-up.

The pharmacy should provide on the external package in these cases a statement of an acceptable period of delay for delivery. The patient or customer should examine the deliv-

ery documentation and ensure that the package has not been subjected to any unacceptable delays during shipping and distribution.

The patient or customer receiving the pharmaceutical articles, either by mail, delivery vehicle from the pharmacy, or directly from the physician or pharmacy should be advised that upon receipt the articles are to be transferred to appropriate storage conditions, as directed by the pharmacy, within two hours of receipt.

The vehicle used for air or surface shipping and distribution of pharmaceutical packages to the patient or customer, especially those requiring low temperatures, should contain the article suitably packaged in containers that maintain the desired storage conditions until it reaches the patient or customer.

The vehicles used for shipping and distribution of pharmaceutical articles to patient or customer, especially those requiring storage at "room" or "controlled room" temperatures should be suitably equipped during extreme temperature conditions such that the packages are not exposed to extremes of temperature either in winter or summer months. In the event that the vehicle is not adequately equipped with air conditioning or heating to protect the product, the product should not be kept in the vehicle for more than two hours. Where appropriate, a monitoring device may be used to ensure that required temperatures are maintained until the package reaches the patient or customer.

If stability studies for the Pharmacopeial preparation indicate that it is particularly sensitive to environmental insults or if appropriate shipping safeguards described in this section are not feasible, then the preparation should be shipped by a different method where such environmental control can be maintained.

Compromised Temperature Conditions

There should be appropriate procedures in the pharmacy that ships the article to the patient or customer to define the action that should be taken in the event that a patient has reported that articles, including any environmentally sensitive preparations, deviated from required storage conditions prior to the point of receipt.

Advice on the suitability of the product for use should be provided to the patient or customer after the manufacturer or supplier's advice has been sought by the pharmacy. If the patient is advised to use the article, such advice should be documented and noted appropriately by the pharmacy. Otherwise, appropriate rearrangements should be made to promptly replace the suspect article. For mail order items, replacement from local pharmacies may be necessary to ensure an uninterrupted supply of medication.

RETURNS OF PHARMACEUTICAL ARTICLES FROM PATIENTS OR CUSTOMERS

The wholesaler, manufacturer, and pharmacy personnel should evaluate the validity of the request for return and maintain an auditable account of the return receipt.

For products in unopened manufacturer's containers that have been at variance during shipment, arrangement may be made to return the products to the manufacturer, wholesaler, or pharmacy within three working days of receipt. The supplier may request records or written confirmation by the patient to show that the product was stored properly while in possession of the customer.

STORAGE OF PHYSICIAN SAMPLES HANDLED BY SALES REPRESENTATIVES IN AUTOMOBILES

Automobile trunks or passenger cabins used for the storage and distribution of physician samples should be validated to determine the temperature profile of the trunk or passenger cabin. Suitable monitoring devices as determined by the sales representative may be placed in different areas of the trunk or passenger cabin on a hot summer and a cold winter day. Measurements should also be made during typical 24-hour periods, and the derived temperature should be used for calculation of mean kinetic temperature at which the sample is stored; see general chapter *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩ for samples of MKT calculations.

If the Pharmacopeial article designated for storage requires storage at controlled room temperature, then suitable measures should be taken to maintain the sample within the allowable limits of the storage parameters.

Environmentally sensitive preparations should not be stored in automobile trunks or passenger cabins. Medications stored in automobile trunks or passenger cabins should be removed at the end of three days. Sales representatives should consider parking automobiles in shaded areas to avoid extreme heat during the summer and in garages to avoid freezing temperatures during the winter.

The use of vouchers from the manufacturer that could be presented to patients to exchange for medications at participating pharmacies is an alternative way of providing drug samples.

STORAGE OF DRUGS IN EMERGENCY MEDICAL SERVICES (EMS) VEHICLES

Ambulances and other emergency medical response vehicles that routinely carry Pharmacopeial articles should be validated to verify that temperature profiles in pharmaceutical storage cabinets are within normal limits. Suitable monitoring devices should be placed in the pharmaceutical cabinet on hot summer and cold winter days. Measurements should also be made during a typical 24-hour period, and the derived temperature should be used for calculation of mean kinetic storage temperature of the sample.

The portable carrying case in which the drugs are kept should be insulated, and when not in use, should be kept in a pharmaceutical storage cabinet.

If the Pharmacopeial article designated for storage requires storage at controlled room temperature, then suitable measures should be taken to maintain the sample within the allowable limits of the storage parameters, and monitoring devices should be in place to record weekly temperatures, and allow calculation of MKT for controlled room temperature storage.

Environmentally sensitive preparations should not be stored in emergency response vehicles unless the cabinet in which the medication is stored is climate controlled. If environmentally sensitive preparations must be kept in the EMS vehicle, then medication supplies should be rotated every three days. Ambulance personnel should consider parking in the shade in the summer or in heated garages in the winter to avoid temperature extremes.

STABILITY, STORAGE, AND LABELING

The design of stability studies of Pharmacopeial articles is based on knowledge of the behavior, properties, and stability of the drug substance and experience gained from clinical formulation studies.[1] The length of the studies and the storage conditions for a Pharmacopeial article should be sufficient to cover storage, shipment, distribution, and subsequent use of a Pharmacopeial article.

The data gathered from ICH accelerated testing or from testing at an ICH intermediate condition may be used to evaluate the effect of short-term excursions outside the label storage conditions such as might occur during shipping.

ICH recommended conditions for solid oral dosage forms are as follows:

— long-term testing: 25 ± 2°C / 60 ± 5% RH for a minimum time period at submission of 12 months.
— accelerated testing: 30° to 40 ± 2°C / 75 ± 5% RH for a minimum time period of 6 months.

Where "significant change" occurs at accelerated testing, additional testing should be performed at intermediate or 30 ± 2°C / 60 ± 5% RH for 6 months. "Significant change" is defined as:

— a 5% potency loss from initial assay value of the batch;
— a specified degradant exceeding its specification limit;
— a product exceeding its pH limits;
— a dissolution time exceeding the specification limits for 12 capsules or tablets; or
— a failure to meet specifications for appearance and physical properties, e.g., color, phase separation, resuspendability, delivery per actuation, caking, hardness, etc.

While stability studies are progressing, mass balance should be maintained to ensure that the assay value and levels of degradation products equal 100% of initial value.

For Pharmacopeial articles intended for storage in a refrigerator, the study conditions for long-term investigation are 5 ± 3° for 12 months minimum time period, and an accelerated condition of 25 ± 2° / 60 ± 5% for 6 months minimum time period. If significant changes occur at the accelerated condition between 3 and 6 months during testing, the proposed retest period should be 5 ± 3° for 12 months minimum (see also ICH Q1 A&B).

For Pharmacopeial articles intended for storage in a freezer, there is only a single long-term storage condition of –20 ± 5° at a 12-month minimum time period. Because there is no abbreviated test condition, the test must be repeated for any products requiring a retest.

For drugs at these specified storage conditions, testing at accelerated conditions may be conducted to address the effect of short-term excursions outside the proposed label storage conditions, e.g., during shipping and distribution, and handling (see ICH Q1 A&B).

[1] See International Conference on Harmonization EWG Q1 A&B; see also FDA *Guidance for Industry: Stability Testing of Drug Substances and Drug Products* (www.fda.gov).

STABILITY OF DRUG PRODUCTS AFTER RECONSTITUTION OR DILUTION

Stability testing of drug products after constitution or dilution should be performed to provide information for the labeling in the preparation, storage conditions, and in-use period of the constituted or diluted product.

- For long-term storage conditions, 25 ± 2°/ 60 ± 5% RH for a minimum time period of 12 months.
- For intermediate storage conditions, 30 ± 2°/ 60 ± 5% RH for a minimum time period of 6 months.
- For accelerated storage conditions, 40 ± 2°/ 75 ± 5% RH for 6 months minimum time period. If significant change occurs at any time during 6-month testing period at accelerated storage conditions, additional testing at the intermediate storage conditions should be conducted and evaluated against "significant change" criteria.

For drugs packaged in impermeable containers, stability studies can be conducted under any controlled or ambient humidity conditions

Drugs packaged in semipermeable containers, especially aqueous-based products, should be evaluated for water loss in addition to physical, chemical, biological, and microbiological stability. These evaluations should be done under conditions of low relative humidity to demonstrate that aqueous-based drug products and/or nonaqueous solvent-based products stored in semipermeable containers can withstand low relative humidity environments.

For both aqueous-based drug and nonaqueous drug products, stability studies include the following:

- For long-term storage conditions, 25 ± 2°/ 40 ± 5% RH for a minimum time period of 12 months.
- For intermediate storage conditions, 30 ± 2°/ 60 ± 5% RH for a minimum time period of 6 months.
- For accelerated storage conditions, 40 ± 2°/ ≤25% RH for a minimum time period of 6 months.

When there is a significant change, other than water loss, intermediate storage testing should be performed at 30 ± 2°/ 60 ± 5% RH for 6 months. For drug products intended for storage in a refrigerator: long-term storage conditions are 5 ± 3° for a 12-month minimum time period; accelerated, 25 ± 2°/ 60 ± 5% RH for 6 months minimum time period. For drug products intended for freezer storage: long-term, –20 ± 5° for 12 months minimum time period.

STATEMENTS/LABELING OF THE IMMEDIATE CONTAINERS OR PACKAGE INSERT

Storage statements should be based on the stability evaluations of the Pharmacopeial drug substances and according to national and international requirements.

Room Temperature Storage Statements—For products with a storage statement reading, "Store at controlled room temperature," the labeling should read as follows on the package insert: "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F). Brief exposure to temperatures up to 40°C (104°F) may be tolerated provided the mean kinetic temperature does not exceed 25°C (77°F); however, such exposure should be minimized."

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On the immediate container label, the following may read for Controlled Room Temperature (CRT): "Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (between 59°F and 86°F)."

Cool Storage Statement—The storage statement for labeling may be as follows: "Store in a cool place, 8°C to 15°C (46°F to 59°F)."

Refrigerator Storage Statement—The storage statement for labeling may be as follows: "Store in a refrigerator, 2°C to 8°C (36°F to 46°F)."

Freezer Storage Statement—The storage statement for labeling may be as follows: "Store in a freezer, –25°C to –10°C (–13°F to 14°F)."

See the *General Notices* for all other applicable storage conditions, such as *Storage Under Nonspecific Conditions* and store in a *Dry Place.* Additional cautionary statements to protect the Pharmacopeial drug product from extreme temperature and humidity conditions may be included on the container label and package insert, as the manufacturer desires.■2S (*USP27*)

BRIEFING

⟨1150⟩ Pharmaceutical Stability. It is proposed to divide the current general information chapter *Pharmaceutical Dosage Forms* ⟨1151⟩ into two chapters: (1) *Pharmaceutical Stability* ⟨1150⟩, which will consist of the section on *Stability* (including the calculation of mean kinetic temperature) that is currently in *Pharmaceutical Dosage Forms* ⟨1151⟩ and (2) *Pharmaceutical Dosage Forms* ⟨1151⟩, which will include the material in the current general information chapter ⟨1151⟩ that deals specifically with dosage forms. By dividing the current chapter into these two separate chapters, the chapter titles will more precisely reference the contents of the chapters. In addition, minor editorial style changes have been made. See also briefing under *Pharmaceutical Dosage Forms* ⟨1151⟩.

(PSD: C. Okeke) RTS—40003-1

Add the following:

■⟨1150⟩ PHARMACEUTICAL STABILITY

The term "stability," with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply throughout the shelf life of the product.

The stability parameters of a drug dosage form can be influenced by environmental conditions of storage (temperature, light, air, and humidity), as well as the package components. Pharmacopeial articles should include required storage conditions on their labeling. These are the conditions under which the expiration date shall apply. The storage requirements specified in the labeling for the article must be observed throughout the distribution of the article (i.e., beyond the time it leaves the manufacturer up to and including its handling by the dispenser or seller of the article to the consumer). Although labeling for the consumer should indicate proper storage conditions, it is recognized that control beyond the dispenser or seller is difficult. The beyond-use date shall be placed on the container label.

Stability Protocols

Stability of manufactured dosage forms must be demonstrated by the manufacturer, using methods adequate for the purpose. Monograph assays may be used for stability testing if they are stability-indicating (i.e., if they accurately differentiate between the intact drug molecules and their degradation products). Stability considerations should include not only the specific compendial requirements, but also changes in physical appearance of the product that would warn users that the product's continued integrity is questionable.

Stability studies on active substances and packaged dosage forms are conducted by means of "real-time," long-term tests at specific temperatures and relative humidities representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned. Labeling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air, and light on its stability. Label temperature storage warnings will both reflect the results of the real-time storage tests and allow for expected seasonal excursions of temperature.

Controlled Room Temperature

Controlled room temperature (see *Storage Temperature and Humidity* in *Preservation, Packaging, Storage, and Labeling* under *General Notices and Requirements*) delineates the allowable tolerance in storage circumstances at any location in the chain of distribution (e.g., pharmacies, hospitals, and warehouses). This terminology also allows patients or consumers to be counseled as to appropriate storage for the product. Products may be labeled either to store at "Controlled room temperature" or to store at temperatures "up to 25°" where labeling is supported by long-term stability studies at the designated storage condition of 25°. *Controlled room temperature* limits the permissible excursions to those consistent with the maintenance of a mean kinetic temperature calculated to be not more than 25°. See *Mean Kinetic Temperature.* The common international guideline for long-term stability studies specifies 25 ± 2° at 60 ± 5% relative humidity. Accelerated studies are specified at 40 ± 2° and at 75 ± 5% relative humidity. Accelerated studies also allow the interpretation of data and information on short-term spikes in storage conditions in addition to the excursions allowed by controlled room temperature.

The term "room temperature" is used in different ways in different countries, and for products to be shipped outside the continental U.S. it is usually preferable for product labeling to refer to a maximum storage temperature or temperature range in degrees Celsius.

Mean Kinetic Temperature

Mean Kinetic Temperature (MKT) is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, MKT may be considered as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation. It is not a simple arithmetic mean. MKT is calculated from temperatures in a storage facility. The temperatures for calculating MKT

can be conveniently collected using electronic devices that measure temperatures at frequent intervals (e.g., every 15 minutes). MKT can be calculated directly or the data can be downloaded to a computer for processing. For dispensing sites, such as pharmacies and hospitals, where the use of such instruments may not be feasible, devices such as high-low thermometers capable of indicating weekly high and low temperatures over a 52-week period may be employed. The arithmetic mean of the weekly high and low temperatures is then used in the calculation of MKT. MKT is calculated by the following equation (derived from the Arrhenius equation):

$$T_k = \frac{\Delta H/R}{-ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)},$$

in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144 kJ · mole^{-1} (unless more accurate information is available from experimental studies); R is the universal gas constant, 8.3144 × 10^{-3} kJ · mole^{-1} · degree^{-1}; T_1 is the value for the temperature recorded during the first time period, e.g., the first week; T_2 is the value for the temperature recorded during the second time period, e.g., second week; and T_n is the value for the temperature recorded during the nth time period, e.g., nth week, n being the total number of storage temperatures recorded (minimum of 52 weekly entries) during the annual observation period. [NOTE—All temperatures, T, are absolute temperatures in degrees Kelvin (K).]

The following is an example of a typical storage and distribution temperature range in Kelvin degrees and the conversion factors used to convert this range into degrees Fahrenheit and Celsius.

Kelvin (K)	Fahrenheit (°F)	Celsius (°C)
288.1–303.1	59–86	15–30

Conversion Factors:

Fahrenheit to Kelvin = {[(°F – 32) × 5/9] + 273.1}

Celsius to Kelvin = 273.1 + °C

Fahrenheit to Celsius = [(°F – 32) × 5/9]

Climatic Zones

For convenience in planning for packaging and storage, and for stability studies, international practice identifies four climatic zones, which are described in *Table 1*. The United States, Europe, and Japan are characterized by zones I and II. The values in *Table 1* are based on observed temperatures and relative humidities, both outside and in rooms, from which mean kinetic temperatures and average humidity values are calculated.[1] Derived values are based on inspection of data from individual cities and on allowances for a margin of safety in assignment of these specified conditions.

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[1] The source of the data and information in *Table 1* is the International Conference on Harmonization sponsored by the International Federation of Pharmaceutical Manufacturers Associations.

Table 1. International Climatic Zones

	Calculated Data				Derived Data		
Climatic Zone	°C*	°C MKT**	% RH	mbar***	°C	% RH	mbar
I. *Temperate* United Kingdom Northern Europe Canada Russia	20.0	20.0	42	9.9	21	45	11.2
II. *Mediterranean, Subtropical* United States Japan Southern Europe (Portugal-Greece)	21.6	22.0	52	13.5	25	60	19.0
III. *Hot, Dry* Iran Iraq Sudan	26.4	27.9	35	11.9	30	35	15.0
IV. *Hot, Humid* Brazil Ghana Indonesia Nicaragua Philippines	26.7	27.4	76	26.6	30	70	30.0

* Data recorded as <19° calculated as 19°.
** Calculated mean kinetic temperature.
*** Partial pressure of water vapor.

A discussion of aspects of drug product stability that are of primary concern to the pharmacist in the dispensing of medications may be found under *Stability Considerations in Dispensing Practice* ⟨1191⟩.

Inasmuch as this chapter is for purposes of general information only, no statement herein is intended to modify or supplant any of the specific requirements pertinent to pharmaceutical preparations, which are given elsewhere in this Pharmacopeia.■2S (*USP27*)

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BRIEFING

⟨**1151**⟩ **Pharmaceutical Dosage Forms,** *USP 26* page 2396. It is proposed to delete from this general information chapter the section on *Stability* (including calculations of mean kinetic temperature) and to include this material in a new general information chapter, *Pharmaceutical Stability* ⟨1150⟩. See also briefing under *Pharmaceutical Stability* ⟨1150⟩.

(PSD: C. Okeke) RTS—40012-01

Delete the following:

▪~~STABILITY~~

~~The term "stability," with respect to a drug dosage form, refers to the chemical and physical integrity of the dosage unit, and, when appropriate, the ability of the dosage unit to maintain protection against microbiological contamination. The shelf life of the dosage form is the time lapse from initial preparation to the specified expiration date. The monograph specifications of identity, strength, quality, and purity apply throughout the shelf life of the product.~~

~~The stability parameters of a drug dosage form can be influenced by environmental conditions of storage (temperature, light, air, and humidity), as well as the package components. Pharmacopeial articles should include required storage conditions on their labeling. These are the conditions under which the expiration date shall apply. The storage requirements specified in the labeling for the article must be observed throughout the distribution of the article (i.e., beyond the time it leaves the manufacturer up to and including its handling by the dispenser or seller of the article to the consumer). Although labeling for the consumer should indicate proper storage conditions, it is recognized that control beyond the dispenser or seller is difficult. The beyond-use date shall be placed on the container label.~~

~~*Stability Protocols*—Stability of manufactured dosage forms must be demonstrated by the manufacturer by the use of methods adequate for the purpose. Monograph assays may be used for stability testing if they are stability indicating (i.e., if they accurately differentiate between the intact drug molecules and their degradation products). Stability considerations should include not only the specific compendial requirements, but also changes in physical appearance of the product that would warn users that the product's continued integrity is questionable.~~

~~Stability studies on active substances and packaged dosage forms are conducted by means of "real-time," long-term tests at specific temperatures and relative humidities representing storage conditions experienced in the distribution chain of the climatic zone(s) of the country or region of the world concerned. Labeling of the packaged active substance or dosage form should reflect the effects of temperature, relative humidity, air, and light on its stability. Label temperature storage warnings will reflect both the results of the real-time storage tests and also allow for expected seasonal excursions of temperature.~~

~~*Controlled room temperature* (see the *Storage Temperature* section under *General Notices and Requirements—Preservation, Packaging, Storage, and Labeling*) delineates the allowable tolerance in storage circumstances at any location in the chain of distribution (e.g., pharmacies, hospitals, and warehouses). This terminology also allows patients or consumers to be counseled as to appropriate storage for the product. Products may be labeled either to store at "Controlled room temperature" or to store at temperatures "up to 25°" where labeling is supported by long-term stability studies at the designated storage condition of 25°. *Controlled room temperature* limits the permissible excursions to those consistent with the maintenance of a mean kinetic temperature calculated to be not more than 25°. See *Mean Kinetic Temperature.*~~

~~The common international guideline for long-term stability studies specifies 25 ± 2° at 60 ± 5% relative humidity. Accelerated studies are specified at 40 ± 2° and at 75 ± 5% relative humidity. Accelerated studies also allow the interpretation of data and information on short-term spikes in storage conditions in addition to the excursions allowed for by controlled room temperature.~~

~~The term "room temperature" is used in different ways in different countries, and it is usually preferable for product labeling for products to be shipped outside the continental U.S. to refer to a maximum storage temperature or temperature range in degrees Celsius.~~

~~*Mean Kinetic Temperature*—Mean Kinetic Temperature (MKT) is defined as the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, MKT may be considered as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation. It is not a simple arithmetic mean. MKT is calculated from temperatures in a storage facility. It can be conveniently collected using electronic devices that measure temperatures at frequent intervals (e.g., every 15 minutes). MKT can be calculated directly or the data can be downloaded to a computer for processing. For dispensing sites, such as pharmacies and hospitals, where the use of such instruments may not be feasible, devices such as high-low thermometers capable of indicating weekly high and low temperatures over a 52-week period may be employed. The arithmetic mean of the weekly high and low temperatures is then used in the calculation of MKT. MKT is calculated by the following equation (derived from the Arrhenius equation):~~

$$T_k = \frac{\Delta H/R}{-ln\left(\frac{e^{-\Delta H/RT_1} + e^{-\Delta H/RT_2} + \ldots + e^{-\Delta H/RT_n}}{n}\right)},$$

~~in which T_k is the mean kinetic temperature; ΔH is the heat of activation, 83.144 kJ·mole^{-1} (unless more accurate information is available from experimental studies); R is the universal gas constant, 8.3144 × 10^{-3} kJ·mole^{-1}·degree^{-1}; T_1 is the value for the temperature recorded during the first time period, e.g., the first week; T_2 is the value for the temperature recorded during the second time period, e.g., second week; T_n is the value for the temperature recorded during the nth time period, e.g., nth week, n being the total number of storage temperatures recorded (minimum of 52 weekly entries) during the annual observation period, and all temperatures, T, being absolute temperatures in degrees Kelvin (°K).~~

~~The following is an example of a typical storage and distribution temperature range in Kelvin degrees and the conversion factors used to convert this range into degrees Fahrenheit and Celsius.~~

~~Kelvin (°K)~~	~~Fahrenheit (°F)~~	~~Celsius (°C)~~
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~~Conversion Factors:~~
~~Fahrenheit to Kelvin = {[(°F − 32) × 5/9] + 273.1}~~
~~Celsius to Kelvin = 273.1 + °C~~
~~Fahrenheit to Celsius = [(°F − 32) × 5/9]~~

~~*Climatic Zones*—For convenience in planning for packaging and storage, and for stability studies, international practice identifies four climatic zones, which are described in *Table 1*. The United States, Europe, and Japan are characterized by zones I and II. The values in *Table 1* are based on observed temperatures and relative humidities, both outside and in rooms, from which mean kinetic temperatures and average humidity values are calculated.[1] Derived values are based on inspection of data from individual cities and on allowances for a margin of safety in assignment of these specified conditions.~~

~~[1] The source of the data and information in Table 1 is the International Conference on Harmonization sponsored by the International Federation of Pharmaceutical Manufacturers Associations.~~

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Table 1. International Climatic Zones

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III. *Hot, Dry* Iran Iraq Sudan	26.4	27.9	35	11.9	30	35	15.0
IV. *Hot, Humid* Brazil Ghana Indonesia Nicaragua Philippines	26.7	27.4	76	26.6	30	70	30.0

* Data recorded as <19° calculated as 19°.
** Calculated mean kinetic temperature.
*** Partial pressure of water vapor.

A discussion of aspects of drug product stability that are of primary concern to the pharmacist in the dispensing of medications may be found under *Stability Considerations in Dispensing Practice* ⟨1191⟩.

Inasmuch as this chapter is for purposes of general information only, no statement herein is intended to modify or supplant any of the specific requirements pertinent to pharmaceutical preparations, which are given elsewhere in this Pharmacopeia. ■2S (*USP27*)

BRIEFING

⟨1177⟩ Good Packaging Practices. The text of this new general information chapter is based on the information on packaging that was included in the formerly proposed general information chapter *Packaging, Storage, and Distribution of Pharmacopeial Articles* ⟨1141⟩ (see page 493 of *PF* 26(2) [Mar.–Apr. 2000] and page 8458 of *PF* 25(4) [July–Aug. 1999]). Information related to storage and distribution has been moved to *Good Storage and Shipping Practices* ⟨1079⟩, a new chapter proposed elsewhere in this number of *PF*. Other editorial changes have also been made.

(PSD: C. Okeke) RTS—40177-1

Add the following:

■⟨1177⟩ GOOD PACKAGING PRACTICES

This chapter provides general guidance on packaging considerations for Pharmacopeial preparations that may be stored, transported, and distributed. It describes procedures that should be considered to ensure that proper packaging practices are maintained. It does not affect any applicable requirements under good manufacturing practices, state laws governing pharmacy, the *USP General Notices and Requirements* or monographs, or provisions under approved labeling.

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Definitions for storage conditions and packaging are provided in *Preservation, Packaging, Storage, and Labeling* under *General Notices and Requirements*. All equipment used for recording, monitoring, and maintaining these temperatures and humidity conditions should be calibrated on a regular basis. This calibration should be traceable to national or international standards (see also the general information chapter *Monitoring Devices—Time, Temperature, and Humidity* ⟨1118⟩).

CONTAINERS

The monograph packaging and storage statement specifies that the container (primary package) should meet the requirements under *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩, which include the stipulations for determining if a container is "tight" or "well-closed." In most cases, compendial preparations are expected to be packaged in "tight" containers especially if the article is moisture sensitive. In addition, where necessary, the packaging component should protect the preparation from light, reactive gases, solvent loss, microbial contamination, etc. "Tight" and "well-closed" containers are clearly defined in *General Notices and Requirements* (see *Containers* under *Preservation, Packaging, Storage, and Labeling*), whereas testing protocol and moisture permeation limits to determine if the container meets either of these definitions can be found in *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩ for single-unit and multiple-unit containers.

A packaging system is comprised of a container system with its closure. This system may include several layers of protection for the Pharmacopeial preparation along with any sealing devices, delivery devices, labeling, and package inserts. The *General Notices* section also provides definitions for types of packaging systems that contain and protect a Pharmacopeial preparation (i.e., single-unit containers, unit-dose containers, etc.). Stability testing is conducted on the dosage forms packaged in the container–closure system proposed for marketing.

One type of permeation test for multiple-unit containers is described in *Containers—Permeation* ⟨671⟩. This test is intended for drug products being dispensed on prescription in vials with a container-closure system. The results of the test reflect the water vapor permeation through the container and through the closure. Limits have been established to define whether a container for dispensing has tight or well-closed characteristics with regard to water vapor permeation. FDA recommends that manufacturers perform this test on the container-closure system, although it is not specified in *USP*. In this particular test, the inner seal of the manufacturer's container-closure system is removed prior to testing.

Single-unit containers for capsules and tablets under *Containers—Permeation* ⟨671⟩ are measured for water vapor permeation according to the criteria for the four classes of containers (classes A–D).

The *USP* recognizes several official container materials that can be selected on the basis of their properties. Most containers are made of glass or plastic. Glass containers must be evaluated for chemical resistance and light transmission (if indicated) as described in *Containers* ⟨661⟩. In addition, injectable medication containers should be reviewed according to the section on *Packaging* under *Injections* ⟨1⟩. Elastomeric closures should be evaluated separately as described in *Elastomeric Closures for Injection* ⟨381⟩. Plastic containers should be assessed using different criteria for the three types of plastics as described in the following sections under *Container* ⟨661⟩: *Polyethylene Containers* (PE) for dry oral solid dosage forms, *Polyethylene Terephthalate Bottles and Polyethylene Terephthalate G Bottles* (PET, PETG) for liquid oral dosage forms, and *Polypropylene Containers* (PP) for dry solid and liquid oral

dosage forms. As articulated in these sections, plastics should undergo testing for light transmission (if appropriate), water vapor permeation (see also *Containers—Permeation* ⟨671⟩), extraction physiochemical testing, and biological testing (see also *Biological Reactivity Tests, In Vitro* ⟨87⟩ and *Biological Reactivity Tests, In Vivo* ⟨88⟩). For example, testing water vapor permeation for a PE container is conducted by sealing the container with heat-sealed foil laminate and measuring the water permeation in a humid atmosphere. Given that water vapor does not permeate the foil laminate, this test assesses only the properties of the container. The level of protection provided by a packaging system marketed with a heat-sealed foil laminate inner seal (prior to removal of the foil) is approximated by this test. However, in the case of a PET bottle for liquid preparations, water vapor permeation testing is done by filling containers with water and measuring the water loss rate in a dry atmosphere. Additional testing may be required for certain pharmaceutical dosage forms as well.

The container–closure system for the storage or shipment of a bulk liquid drug substance is typically plastic, stainless steel, a glass-lined metal container, or an epoxy-lined metal container with a rugged, tamper-resistant closure. Qualification of the container–closure system for these types of preparations includes evaluation for solvent and gas permeation, light transmittance, closure integrity, ruggedness in shipment, protection against microbial contamination through the closure, and compatability and safety of the packaging components as appropriate (see *Containers* ⟨661⟩).

Other information on container–closure systems may be found in FDA's *Guidance for Container Closure System for Packaging Human Drugs and Biologics,* www.fda.gov.

PACKAGING

Packaging for Pharmacopeial articles can be divided into categories according to terminology generally accepted by industry. As mentioned earlier, the *General Notices* section provides some definitions for different types of containers classified by their characteristics and uses. In addition, the ASTM Committee Dl0 on packaging publishes terminology, practices, test methods, specifications, guides, and classifications for testing and evaluating packaging (see ASTM D99695, "Standard Terminology of Packaging and Distribution Environments"). Under certain rules and guidelines (e.g., such as 49 CFR, Dangerous Goods, and others), however, alternate terminology is used for the components described below. For terminology pertaining to repackaging processes, refer to *Packaging Practice—Repackaging a Single Solid Oral Drug Product into a Unit-Dose Container* ⟨1146⟩.

Primary Container—This container is in direct contact with the Pharmacopeial preparation. The purpose of a primary container, also referred to as an immediate container, is to protect the preparation from environmental hazards during storage and handling. In some cases, the primary container is also a specialized delivery system, such as an aerosol or a metered-dose dispenser (see *Pharmaceutical Dosage Forms* ⟨1151⟩). For the majority of oral dosage forms, the primary container consists of a cap and a bottle or a blister or pouch package that can be made from many different materials, including glass, plastic, single or laminated flexible materials, and metal. All components of the primary container must meet the requirements under 21 CFR for direct food contact and, where applicable, the *USP* requirements under *Containers* ⟨661⟩ and *Containers—Permeation* ⟨671⟩. A full description of the primary container is included under the "Container/Closure

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System'' section of the New Drug Application (NDA), Abbreviated New Drug Application (ANDA), or other classes of FDA submissions.

Critical Secondary Container—This container is not in direct contact with the article, but it provides essential product stability protection. For example, a primary container may be packed inside a critical secondary container such as a pouch to provide moisture, gas, light, or microbial protection not afforded by the primary container. A description of the critical secondary container is included under the ''Container/Closure System'' section of the NDA, ANDA, or other classes of FDA submissions.

Secondary Container—This container encloses one or more primary containers. A secondary container is not always present. If used, it is usually designed for the final market presentation. Secondary containers are often used simply to carry required labeling or to keep individual primary containers together with delivery systems or other add-on features. Secondary containers can also provide protection against damage in the handling and distribution system. The most common secondary container is the standard folding carton. Some products, such as syringes, may be placed in trays prior to packing in a carton. Secondary container materials are not included in the container and closure description and require neither stability studies nor prior approval when making a change in the materials used.

Additional Packaging—A wide variety of additional packaging, such as trays and display cartons, may be used to hold primary containers.

Unit of Sale—This may be an individual bottle, a carton containing one or more bottles, or a tray with multiple primary containers. A unit of sale may contain more than one item for individual sale. For example, a display tray may have multiples of a single article or a variety of related articles from a single manufacturer, each intended for individual sale. The individual item intended for sale is referred to as a stock-keeping-unit (SKU). SKUs are distinguished by a discrete National Drug Code (NDC). Over-the-counter (OTC) articles contain a Universal Product Code (UPC) for all SKUs. A prescription SKU may be intended for final consumer use and may not be repackaged by a pharmacy. Such packages, often called ''unit of issue'' or ''unit of use,'' require child-resistant (CR) packaging as described under 16 CFR 1700, ''Poison Prevention Packaging,'' except for packages exempted by the Consumer Product Safety Commission. The CR feature is typically incorporated by the manufacturer (see *Packaging—Unit of Use* ⟨1136⟩). OTC articles are regulated under the same rule, but only if they contain certain active ingredients above specified limits. Any regulated product shipped via the United States Postal Service (USPS) must meet the USPS rules under 39 CFR 111.

Final Exterior Package—This is typically a corrugated fiberboard box (case) or a wrapper. The shipping case label is affixed to this outermost layer and incorporates all of the bar codes required by the National Wholesale Druggists' Association (NWDA). This final package is normally shipped on pallets to distribution centers, wholesalers, and other large-volume customers. The manufacturer may or may not intend that this package enter the small-package-shipping environment as an individual unit without further protection.

Especially with fiberboard boxes, relative humidity (RH) may have a negative effect on the compression strength of the box, causing loads to shift and potentially damage the article or the outer and inner packaging. Articles stored in refrigerators or freezers, which are environments with high RH, are prone to this type of damage when stacked. The problem may be exacerbated by carton design, stacking pattern, or use of low edge-crush-test corrugated fiberboard.

Computer programs are available to determine the acceptable stack height and patterns on the basis of carton weight, style, size, and material. If problems occur, the product manufacturer should be contacted. Source materials and reference information on corrugated fiberboard boxes can be found in the "Fiber Box Handbook" published by the Fiber Box Association.

A wholesaler or other reshipper should not assume that the package received from the manufacturer is suitable for reuse. Many packages are customized for very specific routes and modes of transportation and are not suitable for other applications. Like any other shipping container, insulated cartons and inner protective packaging can be damaged during transit, thus affecting package performance and possibly allowing damage to contents if reused.

ENVIRONMENTAL ISSUES

Packaging materials are regulated by a variety of federal, state, and local rules. In general, most pharmaceutical packaging containers can be recycled within local programs. The use of recycled material in primary containers is governed by the FDA, but it is generally not allowed. Pharmaceutical manufacturers commonly follow the most current Coalition of Northeastern Governors' rules (e.g., Model Toxics in Packaging Legislation) regarding heavy metals in packaging and other environmental issues.

Certain classes of Pharmacopeial articles may require special handling. Such articles include products classified as (1) Dangerous Goods under the Department of Transportation (DOT), state, local, or carrier rules; (2) Controlled drugs under the Drug Enforcement Administration (DEA); or (3) scheduled substances under state regulations.

LABELING

The labeling of shipping containers by manufacturers must be in compliance with the pertinent sections of FDA and DOT rules.

Dangerous Goods—The labeling of shipments classified as *Dangerous Goods,* including all information on the bill of lading or airway bill, must follow the instructions provided by the DOT, the International Air Transport Association (IATA), and the carrier. The exterior package must carry all of the required standard symbols for the class of goods, and the shipping container must comply with the performance standards for the articles enclosed. The shipper of record is responsible for compliance with the Dangerous Goods requirements.

Controlled Substances—When Pharmacopeial preparations that contain DEA-scheduled controlled substances are distributed to a patient directly via the USPS, these articles must be marked and labeled in accordance with USPS Domestic Mail Manual, Regulation Article C023, Section 7.2.■2S (*USP27*)

BRIEFING

⟨**1225**⟩ **Validation of Compendial Methods,** *USP 26* page 2439. The following revisions are based on comments received from the USP Biostatistics Expert Committee.

(PA4: H. Pappa) RTS—39466-1

Change to read:

Test procedures for assessment of the quality levels of pharmaceutical products are subject to various requirements. According to Section 501 of the Federal Food, Drug, and Cosmetic Act, assays and specifications in monographs of the United States Pharmacopeia and the National Formulary constitute legal standards. The Current Good Manufacturing Practice regulations [21 CFR 211.194(a)] require that test methods, which are used for assessing compliance of pharmaceutical products with established specifications, must meet proper standards of accuracy and reliability. Also, according to these regulations [21 CFR 211.194(a)(2)], users of analytical methods described in the USP and the NF are not required to validate accuracy and reliability of these methods, but merely verify their suitability under actual conditions of use. Re-

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cognizing the legal status of USP and NF standards, it is essential, therefore, that proposals for adoption of new or revised compendial analytical ~~methods~~

■procedures■2S (*USP27*)
be supported by sufficient laboratory data to document their validity.

The text of this information chapter harmonizes, to the extent possible, with the Tripartite International Conference on Harmonization (ICH) documents *Validation of Analytical Procedures* and the *Methodology* extension text, which are concerned with analytical procedures included as part of registration applications submitted within the EC, Japan, and the USA. Some aspects (dissolution, drug release), which form part of this chapter, are only dealt with in passing in the ICH documents and are to be discussed in the future. Complete harmonization has not been possible, in part because of different uses of terminology. For example, the ICH use of "procedure" presents difficulty, as this term has a specific and different use throughout the *USP–NF.*

Change to read:

SUBMISSIONS TO THE COMPENDIA

Submissions to the compendia for new or revised analytical ~~methods~~

■procedures■2S (*USP27*)
should contain sufficient information to enable members of the ~~USP Committee of Revision~~

■USP Council of Experts and its Expert Committees■2S (*USP27*)
to evaluate the relative merit of proposed procedures. In most cases, evaluations involve assessment of the clarity and completeness of the description of the analytical ~~methods.~~

■procedures,■2S (*USP27*)
determination of the need for the ~~methods.~~

■procedures,■2S (*USP27*)
and documentation that they have been appropriately validated. Information may vary depending upon the type of method involved. However, in most cases a submission will consist of the following sections.

Rationale—This section should identify the need for the ~~method~~

■procedure■2S (*USP27*)
and describe the capability of the specific ~~method~~

■procedure■2S (*USP27*)
proposed and why it is preferred over other types of determinations. For revised procedures, a comparison should be provided of limitations of the current compendial ~~method~~

■procedure■2S (*USP27*)
and advantages offered by the proposed ~~method.~~

■procedure.■2S (*USP27*)
Proposed Analytical Procedure—This section should contain a complete description of the analytical ~~method~~

■procedure■2S (*USP27*)
sufficiently detailed to enable persons "skilled in the art" to replicate it. The write-up should include all important operational parameters and specific instructions such as preparation of reagents, performance of systems suitability tests, description of blanks used, precautions, and explicit formulas for calculation of test results.

Data Elements—This section should provide thorough and complete documentation of the validation of the analytical ~~method.~~

■procedure.■2S (*USP27*)
It should include summaries of experimental data and calculations substantiating each of the applicable analytical performance characteristics. These characteristics are described in the following section.

Change to read:

VALIDATION

Validation of an analytical ~~method~~

■procedure■2S (*USP27*)
is the process by which it is established, by laboratory studies, that the performance characteristics of the ~~method~~

■procedure■2S (*USP27*)
meet the requirements for the intended analytical applications. Typical analytical performance characteristics that should be considered in the validation of the types of ~~methods~~

■procedures■2S (*USP27*)
described in this document are listed in *Table 1*. Since opinions may differ with respect to terminology and use, each of the performance characteristics is defined in the next section of this chapter along with a delineation of a typical method or methods by which it may be measured.

Table 1. Typical Analytical Characteristics Used in Method Validation.

Accuracy
Precision
Specificity
Detection Limit
Quantitation Limit
Linearity
Range
■Ruggedness■2S (*USP27*)

In the case of compendial ~~methods,~~

■procedures,■2S (*USP27*)
revalidation may be necessary in the following cases: a submission to the USP of a revised analytical ~~method;~~

■procedure;■2S (*USP27*)
or the use of an established general ~~method~~

■procedure■2S (*USP27*)
with a new product or raw material (see below under *Data Elements Required for Assay Validation*).

The ICH documents give guidance on the necessity for revalidation in the following circumstances: changes in the synthesis of the drug substance; changes in the composition of the drug product; and changes in the analytical procedure.

Analytical Performance Characteristics

ACCURACY

Definition—The accuracy of an analytical ~~method~~

■procedure■2S (*USP27*)
is the closeness of test results obtained by that ~~method~~

■procedure■2S (*USP27*)
to the true value. The accuracy of an analytical ~~method~~

■procedure■2S (*USP27*)
should be established across its range.

Determination—In the case of the assay of a drug substance, accuracy may be determined by application of the analytical ~~method~~

■procedure■2S (*USP27*)
to an analyte of known purity (e.g., a Reference Standard) or by comparison of the results of the ~~method~~

■procedure■2S (*USP27*)
with those of a second, well-characterized ~~method,~~

■procedure,■2S (*USP27*)
the accuracy of which has been stated or defined.

In the case of the assay of a drug in a formulated product, accuracy may be determined by application of the analytical ~~method~~

■procedure■2S (*USP27*)
to synthetic mixtures of the drug product components to which known amounts of analyte have been added within the range of the ~~method.~~

■procedure.■2S (*USP27*)
If it is not possible to obtain samples of all drug product components, it may be acceptable either to add known quantities of the analyte to the drug product (i.e., "to spike") or to compare results with those of a second, well-characterized ~~method,~~

■procedure,■2S (*USP27*)
the accuracy of which has been stated or defined.

In the case of quantitative analysis of impurities, accuracy should be assessed on samples (of drug substance or drug product) spiked with known amounts of impurities. Where it is not possible to obtain samples of certain impurities or degradation products, results should be compared with those obtained by an independent ~~method.~~

■procedure.■2S (*USP27*)
In the absence of other information, it may be necessary to calculate the amount of an impurity based on comparison of its response to that of the drug substance; the ratio of the responses of equal amounts of the impurity and the drug substance (response factor) should be used if known.

Accuracy is calculated as the percentage of recovery by the assay of the known added amount of analyte in the sample, or as the difference between the mean and the accepted true value, together with confidence intervals.

The ICH documents recommend that accuracy should be assessed using a minimum of nine determinations over a minimum of three concentration levels, covering the specified range (i.e., three concentrations and three replicates of each concentration).

■Assessment of accuracy can be accomplished in a variety of ways, including evaluating the recovery of the analyte (percent recovery) across the range of the assay, or evaluating the linearity of the relationship between estimated and actual concentrations. The statistically preferred criterion is that the confidence interval for the slope be contained in an interval around 1.0, or alternatively, that the slope be close to 1.0. In either case, the interval or the definition of closeness should be specified in the validation protocol. The acceptance criterion will depend on the assay and its variability and on the product. Setting an acceptance criterion based on the lack of statistical significance of the test of the null hypothesis that the slope is 1.0 is not an acceptable approach.■2S (*USP27*)

PRECISION

Definition—The precision of an analytical ~~method~~

■procedure■2S (*USP27*)
is the degree of agreement among individual test results when the ~~method~~

■procedure■2S (*USP27*)
is applied repeatedly to multiple samplings of a homogeneous sample. The precision of an analytical ~~method~~

■procedure■2S (*USP27*)
is usually expressed as the standard deviation or relative standard deviation (coefficient of variation) of a series of measurements. Precision may be a measure of either the degree of reproducibility or of repeatability of the analytical ~~method~~

■procedure■2S (*USP27*)
under normal operating conditions. In this context, reproducibility refers to the use of the analytical procedure in different laboratories, as in a collaborative study. Intermediate precision expresses within-laboratory variation, as on different days, or with different analysts or equipment within the same laboratory. Repeatability refers to the use of the analytical procedure within a laboratory over a short period of time using the same analyst with the same equipment. For most purposes, repeatability is the criterion of concern in USP analytical procedures, although reproducibility between laboratories or intermediate precision may well be considered during the standardization of a procedure before it is submitted to the Pharmacopeia.

Determination—The precision of an analytical ~~method~~

■procedure■2S (*USP27*)
is determined by assaying a sufficient number of aliquots of a homogeneous sample to be able to calculate statistically valid estimates of standard deviation or relative standard deviation (coeffi-

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cient of variation). Assays in this context are independent analyses of samples that have been carried through the complete analytical procedure from sample preparation to final test result.

The ICH documents recommend that repeatability should be assessed using a minimum of nine determinations covering the specified range for the procedure (i.e., three concentrations and three replicates of each concentration or using a minimum of six determinations at 100% of the test concentration).

SPECIFICITY

Definition—The ICH documents define specificity as the ability to assess unequivocally the analyte in the presence of components that may be expected to be present, such as impurities, degradation products, and matrix components. Lack of specificity of an individual analytical procedure may be compensated by other supporting analytical procedures. [NOTE—Other reputable international authorities (IUPAC, ~~AOAC)~~

■AOAC-I)■2S (*USP27*)
have preferred the term "selectivity," reserving "specificity" for those procedures that are completely selective.] For the ~~test or assay methods~~

■tests discussed■2S (*USP27*)
below, the above definition has the following implications:

Identification Tests: ensure the identity of the analyte.

Purity Tests: ensure that all the analytical procedures performed allow an accurate statement of the content of impurities of an analyte (e.g., related substances test, heavy metals limit, organic volatile ~~impurity limit).~~

■impurities).■2S (*USP27*)

Assays: provide an exact result, which allows an accurate statement on the content or potency of the analyte in a sample.

Determination—In the case of qualitative analyses (identification tests), the ability to select between compounds of closely related structure that are likely to be present should be demonstrated. This should be confirmed by obtaining positive results (perhaps by comparison to a known reference material) from samples containing the analyte, coupled with negative results from samples that do not contain the analyte and by confirming that a positive response is not obtained from materials structurally similar to or closely related to the analyte.

In the case of analytical ~~procedure~~

■procedures■2S (*USP27*)
for impurities, specificity may be established by spiking the drug substance or product with appropriate levels of impurities and demonstrating that these impurities are determined with appropriate accuracy and precision.

In the case of the assay, demonstration of specificity requires that it can be shown that the procedure is unaffected by the presence of impurities or excipients. In practice, this can be done by spiking the drug substance or product with appropriate levels of impurities or excipients and demonstrating that the assay result is unaffected by the presence of these extraneous materials.

■For assay or impurity procedures, this can be done alternatively by demonstrating dilution parallelism between the standard and the sample over the same range used for linearity. The responses from the standard and the analyte are plotted against the respective dilutions (or after appropriate mathematical transformation, if necessary) and the two dilution curves are shown to be parallel within the limits of variation determined by the preset confidence interval for the procedure.■2S (*USP27*)

If impurity or degradation product standards are unavailable, specificity may be demonstrated by comparing the test results of samples containing impurities or degradation products to a second well-characterized procedure (e.g., a Pharmacopeial or other validated procedure). These comparisons should include samples stored under relevant stress conditions (e.g., light, heat, humidity, acid/base hydrolysis, oxidation). In the case of the assay, the results should be compared; in the case of chromatographic impurity tests, the impurity profiles should be compared.

The ICH documents state that when chromatographic procedures are used, representative chromatograms should be presented to demonstrate the degree of selectivity, and peaks should be appropriately labeled. Peak purity tests (e.g., using diode array or mass spectrometry) may be useful to show that the analyte chromatographic peak is not attributable to more than one component.

DETECTION LIMIT

Definition—The detection limit is a characteristic of limit tests. It is the lowest amount of analyte in a sample that can be detected, but not necessarily quantitated, under the stated experimental conditions. Thus, limit tests merely substantiate that the amount of analyte is above or below a certain level. The detection limit is usually expressed as the concentration of analyte (e.g., percentage, parts per billion) in the sample.

Determination—For noninstrumental ~~methods,~~

■procedures,■2S (*USP27*)
the detection limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.

For instrumental procedures, the same ~~method~~

■approach■2S (*USP27*)
may be used as for noninstrumental

■procedures.■2S (*USP27*)
In the case of ~~methods~~

■procedures■2S (*USP27*)
submitted for consideration as official compendial ~~methods,~~

■procedures,■2S (*USP27*)
it is almost never necessary to determine the actual detection limit. Rather, the detection limit is shown to be sufficiently low by the analysis of samples with known concentrations of analyte above and below the required detection level. For example, if it is required to detect an impurity at the level of 0.1%, it should be demonstrated that the procedure will reliably detect the impurity at that level.

In the case of instrumental analytical procedures that exhibit background noise, the ICH documents describe a common approach, which is to compare measured signals from samples with known low concentrations of analyte with those of blank samples. The minimum concentration at which the analyte can reliably be detected is established. Typically acceptable signal-to-noise ratios are 2:1 or 3:1. Other approaches depend on the determination of the slope of the calibration curve and the standard deviation of re-

sponses. Whatever method is used, the detection limit should be subsequently validated by the analysis of a suitable number of samples known to be near, or prepared at, the detection limit.

QUANTITATION LIMIT

Definition—The quantitation limit is a characteristic of quantitative assays for low levels of compounds in sample matrices, such as impurities in bulk drug substances and degradation products in finished pharmaceuticals. It is the lowest amount of analyte in a sample that can be determined with acceptable precision and accuracy under the stated experimental conditions. The quantitation limit is expressed as the concentration of analyte (e.g., percentage, parts per billion) in the sample.

Determination—For noninstrumental ~~methods,~~

■procedures,■2S (*USP27*)
the quantitation limit is generally determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be determined with acceptable accuracy and precision.

For instrumental procedures, the same ~~methods~~

■approach■2S (*USP27*)
may be used as for noninstrumental

■procedures.■2S (*USP27*)
In the case of ~~methods~~

■procedures■2S (*USP27*)
submitted for consideration as official compendial ~~methods,~~

■procedures,■2S (*USP27*)
it is almost never necessary to determine the actual quantitation limit. Rather, the quantitation limit is shown to be sufficiently low by the analysis of samples with known concentrations of analyte above and below the quantitation level. For example, if it is required to assay an analyte at the level of 0.1 mg per tablet, it should be demonstrated that the ~~method~~

■procedure■2S (*USP27*)
will reliably quantitate the analyte at that level.

In the case of instrumental analytical ~~methods~~

■procedures■2S (*USP27*)
that exhibit background noise, the ICH documents describe a common approach, which is to compare measured signals from samples with known low concentrations of analyte with those of blank samples. The minimum concentration at which the analyte can reliably be quantified is established. A typically acceptable signal-to-noise ratio is 10:1. Other approaches depend on the determination of the slope of the calibration curve and the standard deviation of responses. Whatever ~~method~~

■approach■2S (*USP27*)
is used, the quantitation limit should be subsequently validated by the analysis of a suitable number of samples known to be near, or prepared at, the quantitation limit.

LINEARITY AND RANGE

Definition of Linearity—The linearity of an analytical ~~method~~

■procedure■2S (*USP27*)
is its ability to elicit test results that are directly, or by a well-defined mathematical transformation, proportional to the concentration of analyte in samples within a given range.

■Thus, in this section, linearity refers to the linearity of the relationship of concentration and assay measurement. In some cases, to attain linearity, the concentration and/or the measurement may be transformed. (Note that the weighting factors used in the regression analysis may change when a transformation is applied.) Possible transformations may include log, square root, or reciprocal, although other transformations are acceptable. If linearity is not attainable, a nonlinear model may be used. The goal is to have a model, whether linear or nonlinear, that describes closely the concentration-response relationship.■2S (*USP27*)

Definition of Range—The range of an analytical ~~method~~

■procedure■2S (*USP27*)
is the interval between the upper and lower levels of analyte (including these levels) that have been demonstrated to be determined with a suitable level of precision, accuracy, and linearity using the ~~method~~

■procedure■2S (*USP27*)
as written. The range is normally expressed in the same units as test results (e.g., percent, parts per million) obtained by the analytical ~~method.~~

■procedure.■2S (*USP27*)

Determination of Linearity and Range—Linearity should be established across the range of the analytical procedure. It should be established initially by visual examination of a plot of signals as a function of analyte concentration of content. If there appears to be a linear relationship, test results should be established by appropriate statistical methods (e.g., by calculation of a regression line by the method of least squares). ~~In some cases, to obtain linearity between the response of an analyte and its concentration, the test data may have to be subjected to a mathematical transformation.~~

■■2S (*USP27*)
Data from the regression line itself may be helpful to provide mathematical estimates of the degree of linearity. The correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares should be submitted.

The range of the ~~method~~

■procedure■2S (*USP27*)
is validated by verifying that the analytical ~~method~~

■procedure■2S (*USP27*)
provides acceptable precision, accuracy, and linearity when applied to samples containing analyte at the extremes of the range as well as within the range.

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ICH recommends that, for the establishment of linearity, a minimum of five concentrations normally be used. It is also recommended that the following minimum specified ranges should be considered:

Assay of a Drug Substance (or a finished product): from 80% to 120% of the test concentration.

Determination of an Impurity: from 50% to 120% of the ~~specification.~~

■acceptance criterion.■2S (*USP27*)

For Content Uniformity: a minimum of 70% to 130% of the test concentration, unless a wider or more appropriate range, based on the nature of the dosage form (e.g., metered-dose inhalers) is justified.

For Dissolution Testing: ±20% over the specified range (e.g., if the ~~specifications~~

■acceptance criteria■2S (*USP27*)
for a controlled-release product cover a region from 20%, after 1 hour, and up to 90%, after 24 hours, the validated range would be 0% to 110% of the label claim).

RUGGEDNESS

Definition—The ruggedness of an analytical ~~method is the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of conditions, such as different laboratories, different analysts, different instruments, different lots of reagents, different elapsed assay times, different assay temperatures, different days, etc. Ruggedness is normally expressed as the lack of influence on test results of operational and environmental variables of the analytical method. Ruggedness is a measure of reproducibility of test results under the variation in conditions normally expected from laboratory to laboratory and from analyst to analyst.~~

■procedure is the lack of influence on test results obtained by the analysis of the same samples under a variety of conditions, such as different analysts, different instruments, different lots of reagents, different elapsed assay times, different days, and other operational and environmental variables external to the analytical procedure documentation.■2S (*USP27*)

Determination—The ruggedness of an analytical ~~method~~

■procedure■2S (*USP27*)
is determined by analysis of aliquots from homogeneous lots ~~in different laboratories,~~

■■2S (*USP27*)
by different analysts, using operational and environmental conditions that may differ but are still within the specified parameters of the assay. The degree of reproducibility of test results is then determined as a function of the assay variables. This reproducibility may be compared to the precision of the assay under normal conditions to obtain a measure of the ruggedness of the analytical ~~method.~~

■procedure.■2S (*USP27*)

ROBUSTNESS

Definition—The robustness of an analytical ~~method~~

■procedure■2S (*USP27*)
is a measure of its capacity to remain unaffected by small but deliberate variations in ~~method parameters and provides an indication of its reliability~~

■procedural parameters listed in the procedure documentation and provides an indication of its suitability■2S (*USP27*)
during normal usage.

SYSTEM SUITABILITY

If measurements are susceptible to variations in analytical conditions, these should be suitably controlled, or a precautionary statement should be included in the ~~method.~~

■procedure.■2S (*USP27*)
One consequence of the evaluation of robustness and ruggedness should be that a series of system suitability parameters is established to ensure that the validity of the analytical ~~method~~

■procedure■2S (*USP27*)
is maintained whenever used. Typical variations are the stability of analytical solutions, different equipment, and different analysts. In the case of liquid chromatography, typical variations are the pH of the mobile phase, the mobile phase composition, different lots or suppliers of columns, the temperature, and the flow rate. In the case of gas chromatography, typical variations are different lots or suppliers of columns, the temperature, and the flow rate.

System suitability tests are based on the concept that the equipment, electronics, analytical operations, and samples to be analyzed constitute an integral system that can be evaluated as such. System suitability test parameters to be established for a particular ~~method~~

■procedure■2S (*USP27*)
depend on the type of ~~method~~

■procedure■2S (*USP27*)
being evaluated. They are especially important in the case of chromatographic ~~methods, and submissions~~

■procedures. Submissions■2S (*USP27*)
to the USP should make note of the requirements under the *System Suitability* section in the general test chapter *Chromatography* ⟨621⟩.

Data Elements Required for ~~Assay~~

■■2S (*USP27*)

Validation

Compendial ~~assay procedures~~

■test requirements■2S (*USP27*)
vary from highly exacting analytical determinations to subjective evaluation of attributes. Considering this ~~variety of assays,~~

■broad variety,■2S (*USP27*)

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it is only logical that different test ~~methods~~

■procedures■2S (*USP27*)
require different validation schemes. This chapter covers only the most common categories of ~~assays~~

■tests■2S (*USP27*)
for which validation data should be required. These categories are as follows:

Category I—Analytical ~~methods~~

■procedures■2S (*USP27*)
for quantitation of major components of bulk drug substances or active ingredients (including preservatives) in finished pharmaceutical products.

Category II—Analytical ~~methods~~

■procedures■2S (*USP27*)
for determination of impurities in bulk drug substances or degradation compounds in finished pharmaceutical products. These ~~methods~~

■procedures■2S (*USP27*)
include quantitative assays and limit tests.

Category III—Analytical ~~methods~~

■procedures■2S (*USP27*)
for determination of performance characteristics (e.g., dissolution, drug release).

Category IV—Identification tests.

For each ~~assay~~

■■2S (*USP27*)
category, different analytical information is needed. Listed in Table 2 are data elements that are normally required for each of ~~the categories of assays.~~

■these categories.■2S (*USP27*)

Table 2. Data Elements Required for ~~Assay~~

■■2S (*USP27*)
Validation

Analytical Performance Characteristics	~~Assay~~ ■■2S (*USP27*) Category I	~~Assay~~ ■■2S (*USP27*) Category II		~~Assay~~ ■■2S (*USP27*) Category III	~~Assay~~ ■■2S (*USP27*) Category IV
		Quantitative	Limit Tests		
Accuracy	Yes	Yes	*	*	No
Precision	Yes	Yes	No	Yes	No
Specificity	Yes	Yes	Yes	*	Yes
Detection Limit	No	No	Yes	*	No
Quantitation Limit	No	Yes	No	*	No
Linearity	Yes	Yes	No	*	No
Range	Yes	Yes	*	*	No
■Ruggedness	Yes	Yes	Yes	Yes	Yes■2S (*USP27*)

* May be required, depending on the nature of the specific test.

Already established general ~~assays and tests (e.g., titrimetric method of water determination, bacterial endotoxins test)~~

■procedures (e.g., titrimetric determination of water, bacterial endotoxins) ■2S (*USP27*)
should be revalidated to verify their accuracy (and absence of possible interference) when used for a new product or raw material.

The validity of an analytical ~~method~~

■procedure■2S (*USP27*)
can be verified only by laboratory studies. Therefore, documentation of the successful completion of such studies is a basic requirement for determining whether a ~~method~~

■procedure■2S (*USP27*)
is suitable for its intended application(s). Appropriate documentation should accompany any proposal for new or revised compendial analytical procedures.

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BRIEFING

⟨1231⟩ Water for Pharmaceutical Purposes, *USP 26* page 2445. This chapter has been recognized as an authoritative resource for the pharmaceutical water treatment and analysis industry. It is the only USP source of recommendations for the microbial testing of pharmaceutical waters applied in the regulatory arena. At the USP Open Conference on Microbiological Compendial Issues in 1996, attendees recommended that this chapter provide more information on water chemistry. Also, since the establishment of the chapter, it became evident that additional definitions, clarifications, water treatment methodologies, etc., would be useful. During the past two years, a Committee member developed this extensive revision proposal and, after a formal review by the Committee, it was approved for *PF* publication. This is a general information chapter; however, its applications give it special status. The Committee, therefore, encourages public comment. Please direct all communications to Mr. Frank Barletta, USP Information and Standards Development.

(PW: F. Barletta) RTS—39138-2

Change to read:

⟨1231⟩ WATER FOR PHARMACEUTICAL PURPOSES

~~Water is the most widely used substance, raw material, or ingredient in the production, processing, and formulation of compendial articles. Control of the microbiological quality of these waters is important because proliferation of microorganisms ubiquitous to water may occur during the purification, storage, and distribution of this substance. If water is used in the final product, these microorganisms or their metabolic products may eventually cause adverse consequences.~~

~~Water that is used in the early stages of the production of drug substances and that is the source or feed water for the preparation of the various types of purified waters must meet the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the Environmental Protection Agency (EPA). Comparable regulations for drinking water of the European Union or Japan are acceptable. These requirements ensure the absence of coliforms, which, if determined to be of fecal origin, may portend or indicate the presence of other microorganisms of fecal origin, including viruses that may be pathogenic for humans. On the other hand, meeting these National Drinking Water Regulations would not rule out the presence of other microorganisms, which, while not considered a major public health concern, could, if present, constitute a hazard or be considered undesirable in a drug substance or formulated product. For this reason, there are many different grades of pharmaceutical waters.~~

~~TYPES OF WATER~~

~~**Drinking Water**— Drinking Water is not covered by a compendial monograph but must comply with the quality attributes of the EPA NPDWR or comparable regulations of the European Union or Japan. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of more than one of these sources. Drinking Water may be used in the early stages of chemical synthesis and in the early stages of the cleaning of pharmaceutical manufacturing equipment. It is the prescribed source feed water for the production of pharmaceutical waters. As seasonal variations in the quality attributes of the drinking water supply can occur, processing steps in the production of pharmaceutical waters must be designed for this characteristic.~~

~~**Purified Water**— Purified Water (see *USP* monograph) is used as an excipient in the production of official preparations, in pharmaceutical applications, such as cleaning of certain equipment, and in the preparation of some bulk pharmaceutical chemicals. Purified Water must meet the requirements for ionic and organic chemical purity and must be protected from microbial proliferation. It is prepared using Drinking Water as a feed water and is purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable procedures. Purified Water systems must be validated.~~

~~Purified Water systems that produce, store, and circulate water under ambient conditions are susceptible to the establishment of tenacious biofilms of microorganisms, which can be the source of undesirable levels of viable microorganisms or endotoxins in the effluent water. These systems require frequent sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at the points of use.~~

~~**Sterile Purified Water**— Sterile Purified Water [*USP* monograph to come] is *Purified Water* that is packaged and rendered sterile. It is used in the preparation of nonparenteral compendial dosage forms where a sterile form of *Purified Water* is required.~~

~~**Water for Injection**— Water for Injection (see *USP* monograph) is an excipient in the production of injections and for use in pharmaceutical applications, such as cleaning of certain equipment, and in the preparation of some bulk pharmaceutical chemicals. The source or feed water for this article is Drinking Water, which may have been preliminarily purified but which is finally subjected to distillation or reverse osmosis. It must meet all of the chemical requirements for *Purified Water* and in addition the requirements under *Bacterial Endotoxins Test* 85. It also must be protected from microbial contamination. The system used to produce, store, and distribute Water for Injection must be designed to prevent microbial contamination and the formation of microbial endotoxins, and it must be validated.~~

~~**Sterile Water for Injection**— Sterile Water for Injection (see *USP* monograph) is *Water for Injection* that is packaged and rendered sterile. Sterile Water for Injection is intended for extemporaneous prescription compounding and is distributed in sterile units. It is used as a diluent for parenteral products. It is packaged in single dose containers not larger than 1 liter in size.~~

~~**Bacteriostatic Water for Injection**— Bacteriostatic Water for Injection (see *USP* monograph) is sterile *Water for Injection* to which has been added one or more suitable antimicrobial preservatives. It is intended to be used as a diluent in the preparation of parenteral products. It may be packaged in single dose or multiple dose containers not larger than 30 mL.~~

~~**Sterile Water for Irrigation**— Sterile Water for Irrigation (see *USP* monograph) is *Water for Injection,* packaged in single dose containers of larger than 1 liter in size, that is intended to be delivered rapidly and is rendered sterile. It need not meet the requirement under small volume injections in the chapter *Particulate Matter* 788.~~

~~**Sterile Water for Inhalation**— Sterile Water for Inhalation (see *USP* monograph) is *Water for Injection* that is packaged and rendered sterile and is intended for use in inhalators and in the preparation of inhalation solutions.~~

~~VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE, AND DISTRIBUTION SYSTEMS~~

~~Establishing the dependability of pharmaceutical water purification, storage, and distribution systems requires an appropriate period of monitoring and observation. Ordinarily, few problems are~~

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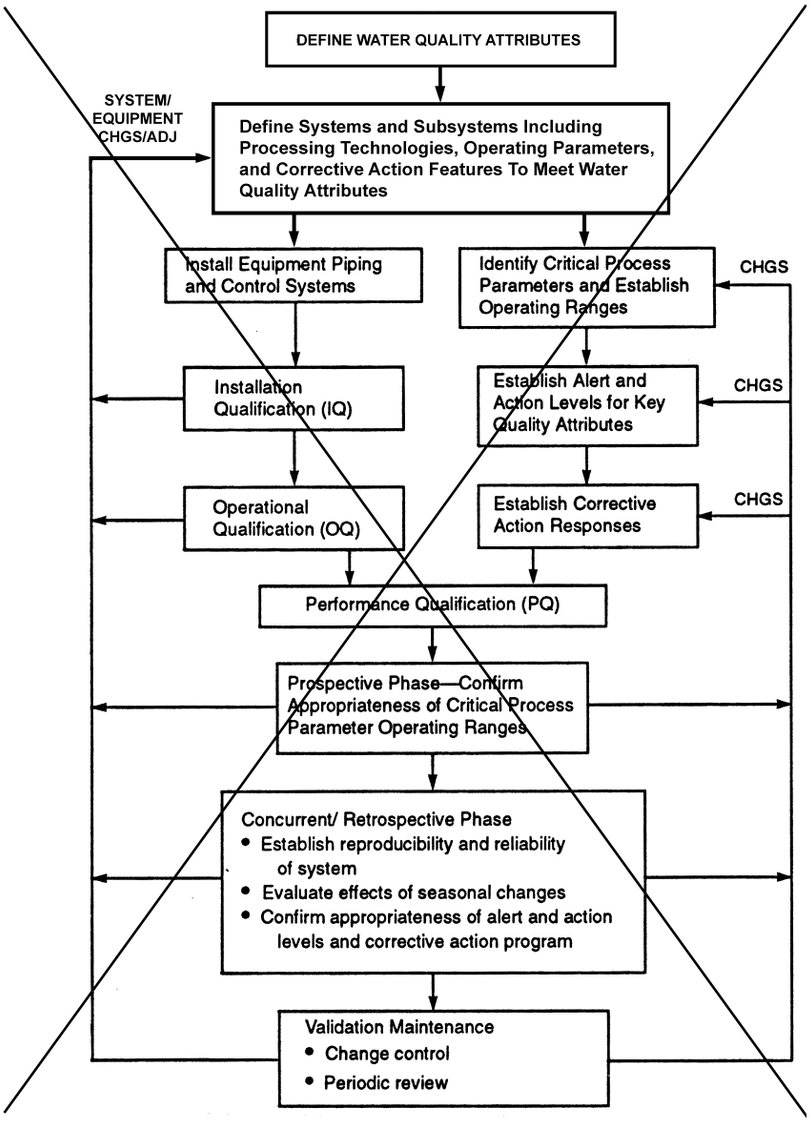
~~encountered in maintaining the chemical purity of *Purified Water* and *Water for Injection*. However, it is more difficult to meet established microbiological quality criteria consistently. A typical program involves intensive daily sampling and testing of major process points for at least one month after operational criteria have been established for each sampling point.~~

~~Validation is the procedure whereby substantiation to a high level of assurance that a specific process will consistently produce a product conforming to an established set of quality attributes is acquired and documented. The validation defines the critical process parameters and their operating ranges. A validation program qualifies the design, installation, operation, and performance of equipment. It begins when the system is defined and moves through several stages: qualification of the installation (IQ), operational qualification (OQ), and performance qualification (PQ). A graphical representation of a typical water system validation life cycle is shown in *Figure 1*. A validation plan for a water system typically includes the following steps:~~

~~(1) Establishing standards for quality attributes and operating parameters.~~



~~Fig. 1. Water system validation life cycle.~~

~~(2) Defining systems and subsystems suitable to produce the desired quality attributes from the available source water.~~

~~(3) Selecting equipment, controls, and monitoring technologies.~~

~~(4) Developing an IQ stage consisting of instrument calibrations, inspections to verify that the drawings accurately depict the as built configuration of the water system and, where necessary, special tests to verify that the installation meets the design requirements.~~

~~(5) Developing an OQ stage consisting of tests and inspections to verify that the equipment, system alerts, and controls are operating reliably and that appropriate Alert and Action Levels~~

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are established. This phase of qualification may overlap with aspects of the next step.

(6) Developing an OQ stage consisting of tests and inspections to vDeveloping a prospective PQ stage to confirm the appropriateness of critical process parameter operating ranges. A concurrent or retrospective PQ is performed to demonstrate system reproducibility over an appropriate time period. During this phase of validation, Alert and Action Levels for key quality attributes and operating parameters are verified.

(7) Developing an OQ stage consisting of tests and inspections to vSupplementing a validation maintenance program (also called continuous validation life cycle) that includes a mechanism to control changes to the water system and establishes and carries out scheduled preventive maintenance including recalibration of instruments. In addition, validation maintenance includes a monitoring program for critical process parameters and a corrective action program.

(8) Instituting a schedule for periodic review of the system performance and requalification.

(9) Completing protocols and documenting Steps 1–8.

PHARMACEUTICAL WATER SYSTEMS

The quality attributes of water for a particular application are dictated by the requirements of its usage. Sequential processing steps that are used for treating water for different pharmaceutical purposes are shown in *Figure 2*. A typical evaluation process to select an appropriate water quality for a particular pharmaceutical purpose is shown in the decision tree in *Figure 3*. These diagrams may be used to assist in defining requirements for specific water uses and in the selection of unit operations.

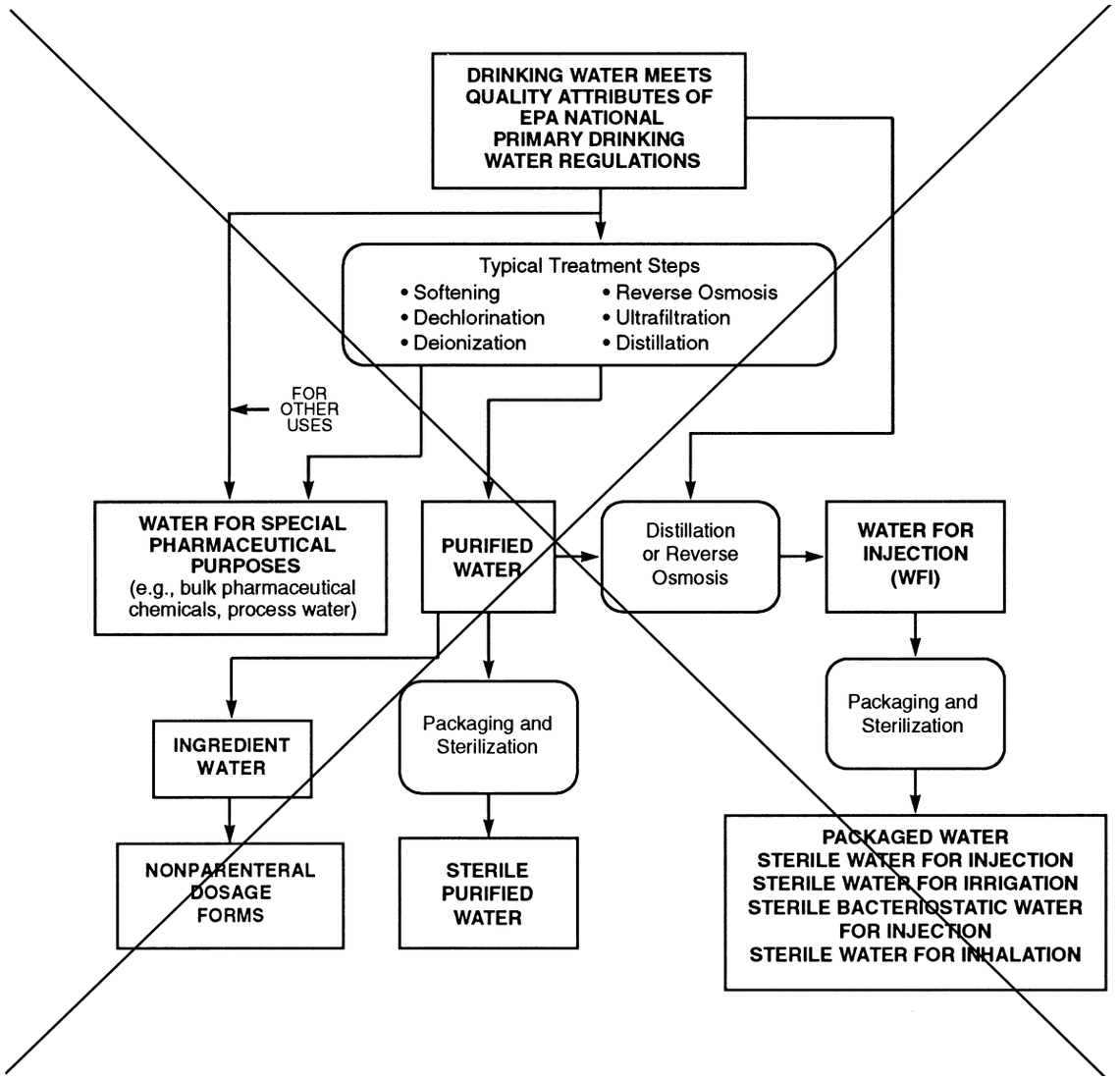
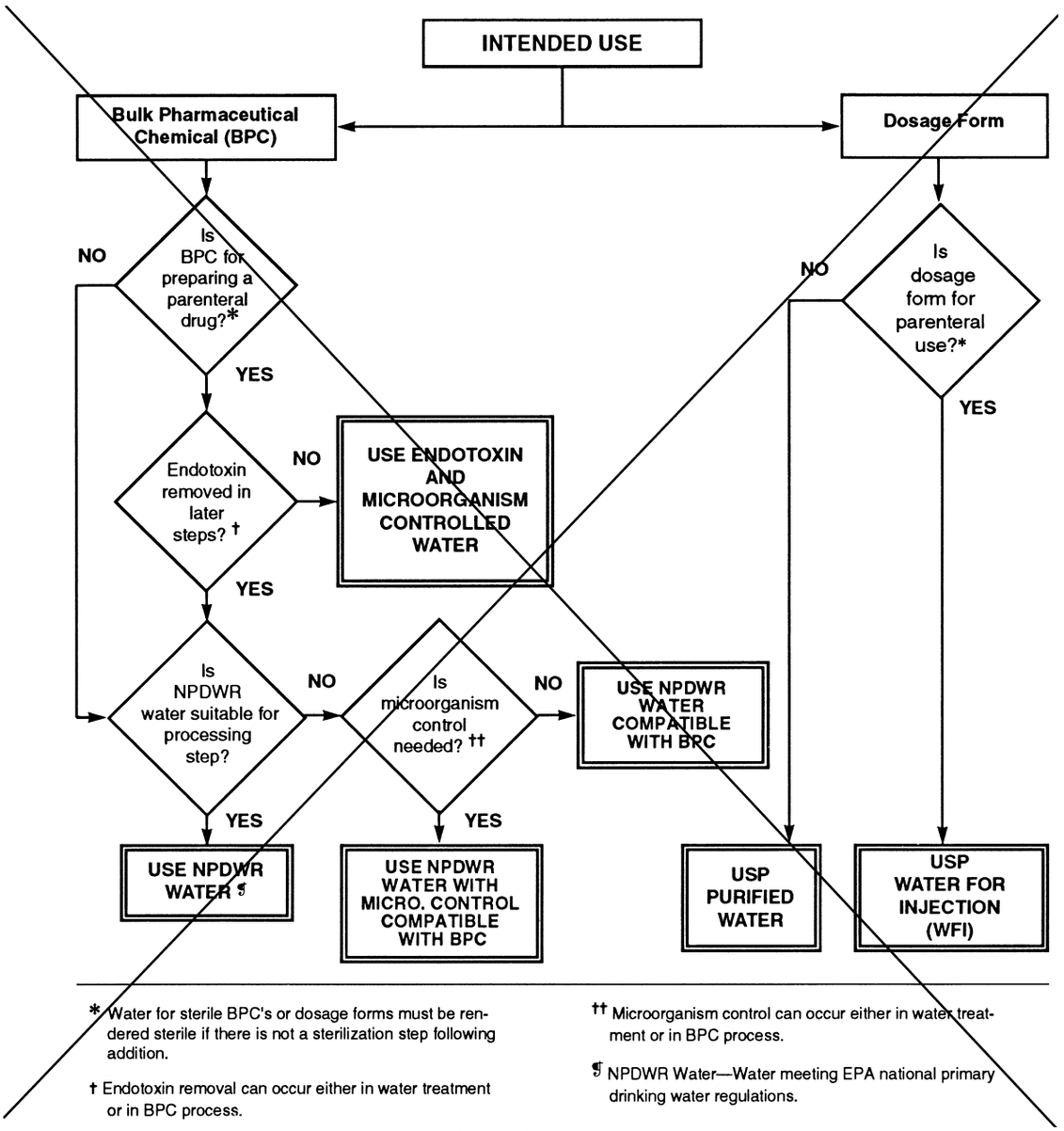


Fig. 2 Water for pharmaceutical purposes.



~~Fig. 3. Selection of water for pharmaceutical purposes.~~

~~PURIFIED WATER AND WATER FOR INJECTION SYSTEMS~~

~~The design, installation, and operation of systems to produce *Purified Water* and *Water for Injection* include similar components, control techniques, and procedures. The quality attributes of both waters differ only in the presence of a bacterial endotoxin requirement for *Water for Injection* and in their methods of preparation, at least at the last stage of preparation. The similarities in the quality attributes provide considerable common ground in the design of water systems to meet either requirement. The critical difference is the degree of control of the system and the final purification steps needed to ensure bacterial and bacterial endotoxin removal.~~

~~Production of pharmaceutical water employs sequential unit operations (processing steps) that address specific water quality attributes and protect the operation of subsequent treatment steps. The final unit operations used to produce *Water for Injection* have been limited to distillation and reverse osmosis. Distillation has a long history of reliable performance and can be validated as a unit operation for the production of *Water for Injection*. Other technologies such as ultrafiltration may be suitable in the production of *Water for Injection*, but at this time experience with this process is not widespread.~~

~~The validation plan should be designed to establish the suitability of the system and to provide a thorough understanding of the purification mechanism, range of operating conditions, required~~

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pretreatment, and the most likely mode of failure. It is also necessary to demonstrate the effectiveness of the monitoring scheme and to establish the requirements for validation maintenance.

Trials conducted in a pilot installation can be valuable in defining the operating parameters and the expected water quality and in identifying failure modes. However, qualification of the specific unit operation can only be performed as part of the validation of the installed operational system.

The selection of specific unit operations and design characteristics for a water system should take into consideration the quality of the feed water, the technology chosen for subsequent processing steps, the extent and complexity of the water distribution system, and the appropriate compendial requirements. For example, in the design of a system for *Water for Injection,* the final process (distillation or reverse osmosis) must have effective bacterial endotoxin reduction capability and must be validated.

The following is a brief description of selected unit operations and the operation and validation concerns associated with them. This review is not comprehensive in that not all unit operations are discussed, nor are all potential problems addressed. The purpose is to highlight issues that focus on the design, installation, operation, maintenance, and monitoring parameters that facilitate water system validation.

Filtration technology plays an important role in water systems, and filtration units are available in a wide range of designs and for various applications. Removal efficiencies differ significantly from coarse filters, such as granular anthracite, quartz, or sand for larger water systems and depth cartridges for smaller water systems, to membrane filters for very small particle control. Unit and system configurations vary widely in type of filtering media and location in the process. (Use of membrane filters is discussed in a later paragraph.)

Granular or cartridge filters are used for prefiltration. They remove solid contaminants from the water supply and protect downstream system components from contamination that can inhibit equipment performance and shorten their effective life. Design and operational issues that may impact performance of depth filters include channeling of the filtering media, blockage from silt, microbial growth, and filtering media loss. Control measures include pressure and flow monitoring, backwashing, sanitizing, and replacing filtering media. An important design concern is sizing of the filter to prevent channeling or media loss resulting from inappropriate water flow rates.

Activated carbon beds adsorb low molecular weight organic material and oxidizing additives, such as chlorine compounds, and remove them from the water. They are used to achieve certain quality attributes and to protect against reaction with downstream stainless steel surfaces, resins, and membranes. The chief operating concerns regarding activated carbon beds include the propensity to support bacteria growth, the potential for hydraulic channeling, the inability to be regenerated *in situ,* and the shedding of bacteria, endotoxins, organic chemicals, and fine carbon particles. Control measures include appropriate high water flow rates, sanitization with hot water or steam, backwashing, testing for adsorption capacity, and frequent replacement of the carbon bed. Alternative technologies such as chemical additives and regenerable organic scavenging devices can be used in place of activated carbon beds.

Chemical additives are used in water systems to control microorganisms by use of chlorine compounds and ozone, to enhance the removal of suspended solids by use of flocculating agents, to remove chlorine compounds, to adjust pH, and to remove carbonate compounds. Subsequent processing steps are required to remove the added chemicals. Control of additives and subsequent monitoring to ensure removal of additives and of any of their reaction products should be designed into the system and included in the monitoring program.

Organic scavenging devices use macroreticular anion exchange resins capable of removing organic material and endotoxins from the water. They can be regenerated with appropriate biocidal caustic solutions. Operating concerns are associated with scavenging capacity and shedding of resin fragments. Control measures include testing of effluent, monitoring performance, and using downstream filters to remove resin fines.

Water softeners remove cations such as calcium and magnesium that interfere with the performance of downstream processing equipment such as reverse osmosis membranes, deionization columns, and distillation units. Water softener resin beds are regenerated with sodium chloride solution (brine). Concerns include microorganism proliferation, channeling due to inappropriate water flow rates, organic fouling of resin, fracture of the resin beads, and contamination from the brine solution used for regeneration. Control measures include recirculation of water during periods of low water use, periodic sanitization of the resin and brine system, use of microbial control devices (e.g., UV and chlorine), appropriate regeneration frequency, effluent monitoring (hardness), and downstream filtration to remove resin fines.

Deionization (DI), electrodeionization (EDI) and Electrodialysis (EDR) are effective methods of improving the chemical quality attributes of water by removing cations and anions.

DI systems have charged resins that require periodic regeneration with an acid and base. Typically, cationic resins are regenerated with either hydrochloric or sulfuric acid, which replace the captured positive ions with hydrogen ions. Anionic resins are regenerated with sodium or potassium hydroxide, which replace captured negative ions with hydroxide ions. Both regenerant chemicals are biocidal and offer a measure of microbial control. The system can be designed so that the cation and anion resins are separated or that they form a mixed bed. Rechargeable resin canisters can also be used for this purpose.

The EDI system uses a combination of mixed resin, selectively permeable membranes, and an electric charge to provide continuous flow (product and waste concentrate) and continuous regeneration. Water enters both the resin section and the waste (concentrate) section. As it passes through the resin, it is deionized to become product water. The resin acts as a conductor enabling the electrical potential to drive the captured cations and anions through the resin and appropriate membranes for concentration and removal in the waste water stream. The electrical potential also separates the water in the resin (product) section into hydrogen and hydroxide ions. This permits continuous regeneration of the resin without the need for regenerant additives.

Electrodialysis (EDR) is a similar process that uses only electricity and selectively permeable membranes to separate, concentrate, and flush the removed ions from the water stream. It, however, is less efficient than EDI because it contains no resin to enhance ion removal and current flow. Also, EDR units require periodic polarity reversal and flushing to maintain operating performance.

Concerns for all forms of deionization units include microbial and endotoxin control, chemical additive impact on resins and membranes, and loss, degradation, and fouling of resin. Issues of concern specific to DI units include regeneration frequency, channeling, complete resin separation for mixed bed regeneration, and mixing air contamination (mixed beds). Control measures vary but typically include recirculation loops, microbial control by UV light, conductivity monitoring, resin testing, microporous filtration of mixing air, microbial monitoring, frequent regeneration to minimize and control microorganism growth, sizing the equipment for suitable water flow, and use of elevated temperatures. Regeneration piping for mixed bed units should be configured to ensure that regeneration chemicals contact all internal surfaces and resins. Rechargeable canisters can be the source of contamination and should be carefully monitored. Full knowledge of previous resin use, minimum storage time between regeneration and use, and appropriate sanitizing procedures are critical factors ensuring proper performance.

Reverse osmosis (RO) units employ a semipermeable membrane and a substantial pressure differential to drive water through the membrane to achieve chemical, microbial, and endotoxin quality improvement. The process streams consist of supply water, product water (permeate), and waste water (reject). Pretreatment and system configuration variations may be necessary depending on

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source water to achieve desired performance and reliability. Concerns associated with the design and operation of RO units include membrane material sensitivity to bacteria and sanitizing agents, membrane fouling, membrane integrity, seal integrity, and the volume of waste water. Failure of membrane or seal integrity will result in product water contamination. Methods of control consist of suitable pretreatment of the water stream, appropriate membrane material selection, integrity challenges, membrane design such as spiral wound to promote flushing action, periodic sanitization, monitoring of differential pressures, conductivity, microbial levels, and total organic carbon. The configuration of the RO unit offers control opportunities by expanding the single pass scheme to parallel staged, reject staged, two pass, and combination designs. An example would be the use of a two pass design to improve reliability, quality, and efficiency. RO units can be used alone or in combination with DI and EDI units for operational and quality enhancements.

Ultrafiltration is another technology that uses a permeable membrane, but unlike RO it works by mechanical separation rather than osmosis. Due to the filtration ability of the membrane, macromolecular and microbial impurities, such as endotoxins, are reduced. This technology may be appropriate as an intermediate or final purification step. Similar to RO, successful performance is dependent upon other system unit operations and system configuration.

Issues of concern include compatibility of membrane material with sanitizing agents, membrane integrity, fouling by particles and microorganisms, cartridge contaminant retention, and seal integrity. Control measures include sanitization, designs capable of flushing the membrane surface, integrity challenges, regular cartridge changes, elevated feed water temperature, and monitoring total organic carbon and differential pressure. Additional flexibility in operation is possible based on the way units are arranged such as in a parallel or series configuration. Care should be taken to avoid stagnant water conditions that could promote microorganism growth in back up or standby units.

Microbial retentive filters (membrane filters) prevent the passage of microorganisms and very small particles. They are used in tank air and inert gas vents and for filtration of compressed air gases used in the regeneration of mixed bed deionization units. Areas of concern are blockage of tank vents by condensed water vapor, which can cause mechanical damage to the tank, and concentration of microorganisms on the surface of the membrane filter, creating the potential for contamination of the tank or deionizer contents. Control measures include the use of hydrophobic filters and heat tracing vent filter housings to prevent vapor condensation. Sterilization of the unit prior to initial use and periodically thereafter or regular filter changes are also recommended control methods. Microbial retentive filters are sometimes incorporated into purification systems or in water distribution piping. This application should be carefully controlled because as noted above, these units can become a source for microbial contamination. The potential exists for the release of microorganisms should the membrane filter rupture or as a result of microbial grow through. Other means of controlling microorganisms and fine particles can be employed in place of membrane filters in the purification and distribution section of water systems. Filters that are intended to be microretentive should be sanitized and integrity tested prior to initial use and at appropriate intervals thereafter.

Positively charged filter media reduce endotoxin levels by electrostatic attraction and adsorption. Application may be unit operation or distribution system related depending upon the microbial control requirements. Filter media that are microbial retentive require the same concerns and controls as indicated in the previous paragraph. Concerns include flow rate, membrane and seal integrity, and retention capacity, which can be affected by the development of a finite charge potential on the filter. Control measures include monitoring differential pressure and endotoxin levels, proper sizing, testing membrane integrity, and configuring units in series to control break through.

Distillation units provide chemical and microbial purification via thermal vaporization, mist elimination, and condensing. A variety of designs are available including single effect, multiple effect, and vapor compression. The latter two configurations are normally used in larger systems because of their generating capacity and efficiency. Distilled water systems may require less rigorous control of feed water quality than do membrane systems. Areas of concern include carry over of impurities, evaporator flooding, stagnant water, pump and compressor seal design, and conductivity (quality) variations during start up and operation. Methods of control consist of reliable mist elimination, visual or automated high water level indication, use of sanitary pumps and compressors, proper drainage, blow down control, and use of on line conductivity sensing with automated diversion of unacceptable quality water to the waste stream.

Storage tanks are included in water distribution systems to optimize processing equipment capacity. Storage also allows for routine maintenance while maintaining continuous supply to meet manufacturing needs. Design and operation considerations are needed to prevent the development of biofilm, to minimize corrosion, to aid in the use of chemical sanitization of the tanks, and to safeguard mechanical integrity. These considerations may include using closed tanks with smooth interiors and the ability to spray the tank head space. This minimizes corrosion and biofilm development and aids in sanitizing thermally or chemically.

Storage tanks require venting to compensate for the dynamics of changing water levels. This can be accomplished with a hydrophobic microbial retentive membrane filter fitted onto an atmospheric vent. Alternatively, an automatic membrane filtered compressed gas pressurization and venting system may be used. Rupture disks equipped with a rupture alarm device serve as a further safeguard for the mechanical integrity of the tank.

Distribution configuration should allow for the continuous flow of water in the piping by means of recirculation or should provide for the periodic flushing of the system. Experience has shown that continuously recirculated systems are easier to maintain.

Pumps should be designed to deliver fully turbulent flow conditions to retard the development of biofilms. Components and distribution lines should be sloped and fitted with drain points so that the system can be completely drained. In distribution systems, where the water is circulated at a high temperature, dead legs and low flow conditions should be avoided, and valved tie in points should have length to diameter ratios of 6 or less. In ambient temperature distribution systems, particular care should be exercised to avoid pocket areas and provide for complete drainage. Water exiting from a loop should not be returned to the system. Distribution design should include the placement of sampling valves in the storage tank and at other locations such as in the return line of the recirculating water system. The primary sampling site for water should be the valves that deliver water to the point of use. Direct connections to processes or auxiliary equipment should be designed to prevent reverse flow into the controlled water system. The distribution system should permit sanitization for microorganism control. The system may be continuously operated at sanitizing conditions or sanitized periodically.

INSTALLATION AND MATERIALS OF CONSTRUCTION AND COMPONENT SELECTION

Installation techniques are important because they can affect the mechanical, corrosive, and sanitary integrity of the system. Valve installation attitude should promote gravity drainage. Pipe supports should provide appropriate slopes for drainage and should be designed to support the piping adequately under worst case thermal conditions. Methods of connecting system components including units of operation, tanks, and distribution piping require careful attention to preclude potential problems.

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Stainless steel welds should provide reliable joints that are internally smooth and corrosion free. Low carbon stainless steel, compatible wire filler, where necessary, inert gas, automatic welding machines, and regular inspection and documentation help to ensure acceptable weld quality. Follow up cleaning and passivation are important for removing contamination and corrosion products and to reestablish the passive corrosion resistant surface. Plastic materials can be fused (welded) in some cases and also require smooth, uniform internal surfaces. Adhesives should be avoided due to the potential for voids and chemical reactions. Mechanical methods of joining, such as flange fittings, require care to avoid the creation of offsets, gaps, penetrations, and voids. Control measures include good alignment, properly sized gaskets, appropriate spacing, uniform sealing force, and the avoidance of threaded fittings.

Materials of construction should be selected to be compatible with control measures such as sanitizing, cleaning, and passivating. Temperature rating is a critical factor in choosing appropriate materials because surfaces may be required to handle elevated operating and sanitization temperatures. Should chemicals or additives be used to clean, control, or sanitize the system, materials resistant to these chemicals or additives must be utilized.

Materials should be capable of handling turbulent flow and elevated velocities without wear on the corrosive barrier impact, such as the passivation related chromium oxide surface of stainless steel. The finish on metallic materials such as stainless steel, whether it be a refined mill finish, polished to a specific grit, or an electropolished treatment, should complement system design and provide satisfactory corrosion and microbial activity resistance. Auxiliary equipment and fittings that require seals, gaskets, diaphragms, filter media, and membranes should exclude materials that permit the possibility of extractables, shedding, and microbial activity.

Insulating materials exposed to stainless steel surfaces should be free of chlorides to avoid the phenomenon of stress corrosion cracking that can lead to system contamination and the destruction of tanks and critical system components.

Specifications are important to ensure proper selection of materials and to serve as a reference for system qualification and maintenance. Information such as mill reports for stainless steel and reports of composition, ratings, and material handling capabilities for nonmetallic substances should be reviewed for suitability and retained for reference.

Component (auxiliary equipment) selection should be made with assurance that it does not create a source for contamination intrusion. Heat exchangers should be double tube sheet or concentric tube design. They should include differential pressure monitoring or utilize heat transfer medium of equal or better quality to avoid problems should leaks develop. Pumps should be of sanitary design with seals that prevent contamination of the water. Valves should have smooth internal surfaces with the seat and closing device exposed to the flushing action of water, such as occurs in diaphragm valves. Valves with pocket areas or closing devices (e.g., ball, plug, gate, globe) that move into and out of a flow area should be avoided.

SANITIZATION

Microbial control in water systems is achieved primarily through sanitization practices. Systems can be sanitized using either thermal or chemical means. In-line UV light at a wavelength of 254 nm can also be used to "sanitize" water in the system continuously.

Thermal approaches to system sanitization include periodic or continuously circulating hot water and the use of steam. These techniques are limited to systems that are compatible with the higher temperatures needed to achieve sanitization, such as stainless steel and some polymer formulations. Although thermal methods control biofilm development, they are not effective in removing established biofilms.

Chemical methods, where compatible, can be used on a wider variety of construction materials. These methods typically employ oxidizing agents such as halogenated compounds, hydrogen peroxide, ozone, or peracetic acid. Halogenated compounds are effective sanitizers but are difficult to flush from the system and tend to leave biofilms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radicals (notably hydroxyl radicals). The short half-life of these compounds, particularly ozone, may require that it be added continuously during the sanitization process. Hydrogen peroxide and ozone rapidly degrade to water and oxygen; peracetic acid degrades to acetic acid in the presence of UV light.

UV light impacts on the development of biofilms by reducing the rate of new microbial colonization in the system; however, it is only partially effective against planktonic microorganisms. Alone, UV light is not an effective tool because it does not eliminate existing biofilm. However, when coupled with conventional thermal or chemical sanitization technologies, it is most effective and can prolong the interval between system sanitizations. The use of UV light also facilitates the degradation of hydrogen peroxide and ozone.

Sanitization steps require validation to demonstrate the capability of reducing and holding microbial contamination at acceptable levels. Validation of thermal methods should include a heat distribution study to demonstrate that sanitization temperatures are achieved throughout the system. Validation of chemical methods require a demonstration of adequate chemical concentrations throughout the system. In addition, when the sanitization process is completed, effective removal of chemical residues must be demonstrated.

The frequency of sanitization is generally dictated by the results of system monitoring. Conclusions derived from the trend analysis of the microbiological data should be used as the alert mechanism for maintenance. The frequency of sanitization should be established such that the system operates in a state of microbiological control and does not exceed Alert Levels.

OPERATION, MAINTENANCE, AND CONTROL

A preventive maintenance program should be established to ensure that the water system remains in a state of control. The program should include (1) procedures for operating the system, (2) monitoring programs for critical quality attributes and operating conditions including calibration of critical instruments, (3) schedule for periodic sanitization, (4) preventive maintenance of components, and (5) control of changes to the mechanical system and to operating conditions.

Operating Procedures—Procedures for operating the water system and performing routine maintenance and corrective action should be written, and they should also define the point when action is required. The procedures should be well documented, detail the function of each job, assign who is responsible for performing the work, and describe how the job is to be conducted.

Monitoring Program—Critical quality attributes and operating parameters should be documented and monitored. The program may include a combination of in-line sensors or recorders (e.g., a conductivity meter and recorder), manual documentation of operational parameters (such as carbon filter pressure drop) and laboratory tests (e.g., total microbial counts). The frequency of sampling, the requirement for evaluating test results, and the necessity for initiating corrective action should be included.

Sanitization—Depending on system design and the selected units of operation, routine periodic sanitization may be necessary to maintain the system in a state of microbial control. Technologies for sanitization are described above.

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Preventive Maintenance—A preventive maintenance program should be in effect. The program should establish what preventive maintenance is to be performed, the frequency of maintenance work, and how the work should be documented.

Change Control—The mechanical configuration and operating conditions must be controlled. Proposed changes should be evaluated for their impact on the whole system. The need to requalify the system after changes are made should be determined. Following a decision to modify a water system, the affected drawings, manuals, and procedures should be revised.

SAMPLING CONSIDERATIONS

Water systems should be monitored at a frequency that is sufficient to ensure that the system is in control and continues to produce water of acceptable quality. Samples should be taken from representative locations within the processing and distribution system. Established sampling frequencies should be based on system validation data and should cover critical areas. Unit operation sites might be sampled less frequently than point of use sites. The sampling plan should take into consideration the desired attributes of the water being sampled. For example, systems for *Water for Injection,* because of their more critical microbiological requirements, may require a more rigorous sampling frequency.

When sampling water systems, special care should be taken to ensure that the sample is representative. Sampling ports should be sanitized and thoroughly flushed before a sample is taken. Samples containing chemical sanitizing agents require neutralization prior to microbiological analysis. Samples for microbiological analysis should be tested immediately or suitably protected to preserve the sample until analysis can begin.

Samples of flowing water are only indicative of the concentration of planktonic (free floating) microorganisms present in the system. Benthic (attached) microorganisms present as biofilms are generally present in greater numbers and are the source of the planktonic population. Microorganisms in biofilms represent a continuous source of contamination and are difficult to sample and quantify. Consequently, the planktonic population is used as an indicator of system contamination levels and is the basis for system Alert Levels. The consistent appearance of elevated planktonic levels is usually an indication of advanced biofilm development in need of remedial control. System control and sanitization are key in controlling biofilm formation and the consequent planktonic population.

MICROBIAL CONSIDERATIONS

The major exogenous source of microbial contamination is source or feed water. Feed water quality must, at a minimum, meet the quality attributes of drinking water for which the level of coliforms are regulated. A wide variety of other microorganisms, chiefly Gram-negative bacteria, may be present. These microorganisms may compromise subsequent purification steps.

Examples of other potential exogenous sources of microbial contamination include unprotected vents, faulty air filters, backflow from contaminated outlets, drain air breaks, and replacement activated carbon and deionizer resins. Sufficient care should be given to system design and maintenance in order to minimize microbial contamination from these sources.

Unit operations can be a major source of endogenous microbial contamination. Microorganisms present in feed water may adsorb to carbon beds, deionizer resins, filter membranes, and other unit operation surfaces and initiate the formation of a biofilm. Biofilm is an adaptive response by certain microorganisms to survive in a low nutrient environment. Microorganisms in a biofilm are protected from the action of many biocides. Downstream colonization can occur when microorganisms are sloughed off and carried in other areas of the water system. Microorganisms may also attach to suspended particles such as carbon bed fines and serve as a source of contamination to subsequent purification equipment and distribution systems.

Another source of endogenous microbial contamination is the distribution system. Microorganisms can colonize pipe surfaces, valves, and other areas. There they proliferate, forming a biofilm, which then provides a continuous source of microbial contamination.

Endotoxins are lipopolysaccharides from the cell envelope that is external to the cell wall of Gram-negative bacteria. Gram-negative bacteria readily form biofilms that can become a source of endotoxins. Endotoxins may either be associated with living microorganisms or fragments of dead microorganisms, or they may be free molecules. The free form of endotoxins may be released from cell surfaces or biofilms that colonize the water system, or they may enter the water system via the feed water. Endotoxin levels may be minimized by controlling the introduction of microorganisms and microbial proliferation in the system. This may be accomplished through the normal exclusion or removal action afforded by various unit operations within the treatment system as well as through system sanitization. Other control methods include the use of ultrafilters or charge-modified filters, either in line or at the point of use. The presence of endotoxins may be monitored as described in the chapter *Bacterial Endotoxins Test* 85.

METHODOLOGICAL CONSIDERATIONS*

The objective of a water system microbiological monitoring program is to provide sufficient information to control the microbiological quality of the water produced. Product quality requirements should dictate water quality needs. An appropriate level of control may be maintained by using data trending techniques and limiting specific contraindicated microorganisms. Consequently, it may not be necessary to detect all of the microorganisms present. The monitoring program and methodology should indicate adverse trends and detect microorganisms that are potentially harmful to the finished product or consumer.

Final selection of method variables should be based on the individual requirements of the system being monitored. It should be recognized that there is no single method that is capable of detecting all of the potential microbial contaminants of a water system. Methods selected should be capable of isolating the numbers and types of organisms that have been deemed significant relative to system control and product impact for each individual system.

Several criteria should be considered when selecting a method to monitor the microbial content of a pharmaceutical water system. These include method sensitivity, range of organisms recovered, sample throughput, incubation period, cost, and technical complexity. An additional consideration is the use of the classical "culture" approaches vs. a sophisticated instrument approach.

THE CLASSICAL CULTURE APPROACH

Classical culture approaches for microbial testing of water include but are not limited to pour plates, spread plates, membrane filtration, and most probable number (MPN) tests. These methods are generally easy to perform, are less expensive, and provide excellent sample processing throughput. Method sensitivity can be increased via the use of larger sample sizes. This strategy is used in the membrane filtration method.

Culture approaches are further defined by the type of medium used in combination with the incubation temperature and duration. This combination should be selected according to the monitoring

* For additional guidance concerning microbial water testing methodology, consult *Standard Methods for the Examination of Water and Wastewater,* 18th Edition, American Public Health Association, Washington DC, 20005.

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needs presented by a specific water system as well as its ability to recover microorganisms that could have a detrimental effect on the product or process.

There are two basic forms of media available for traditional microbiological analysis: "high" nutrient and "low" nutrient. High-nutrient media are intended as general media for the isolation and enumeration of heterotrophic bacteria. Low-nutrient media are beneficial for isolating slow-growing bacteria and bacteria that have been injured by previous exposure to disinfectants and sanitizers such as chlorine. Low-nutrient media may be compared to high-nutrient media, especially during the validation of a water system, in order to determine if any additional numbers or types of bacteria are present so that their impact on the end use may be assessed. Additionally, the efficacy of system controls and sanitization on these slower-growing or impaired bacteria can also be assessed.

Duration and temperature of incubation are also critical aspects of a microbiological test method. Classical methodologies using high-nutrient media have required incubation at 30°C to 35°C for 48 to 72 hours. In certain water systems incubation at lower temperatures (e.g., 20°C to 25°C) and longer periods (e.g., 5 to 7 days) can produce higher counts when compared to classical methods. Whether or not a particular system needs to be monitored using lower incubation temperatures or longer incubation times should be determined during system validation.

The decision to use longer incubation periods should be made after considering the need for timely information and the type of corrective actions required when an Alert or Action Level is exceeded. The advantages gained by incubating for longer times, namely recovery of injured microorganisms, slow growers, or more fastidious microorganisms, should be balanced against the need to have a timely investigation and to take corrective action, as well as the ability of these microorganisms to detrimentally affect products or processes.

"INSTRUMENT" APPROACH

Examples of instrument approaches include microscopic direct counting techniques (e.g., epifluorescence and immunofluorescence), radiometric, impedometric, and biochemically based methodologies. These methods all possess a variety of advantages and disadvantages.

One advantage is their precision and accuracy. In general, instrument approaches often have a shorter lead time for obtaining results, which facilitates timely system control. This advantage, however, is often counterbalanced by limited sample processing throughput due to labor-intensive sample processing or other instrument limitations. In addition, instrumental approaches are destructive in that further isolate manipulation for characterization purposes are precluded. Generally, some form of microbial isolate characterization may be a required element of water system monitoring. Consequently, culturing approaches have traditionally been preferred over instrumental approaches because they offer a balance of desirable test attributes and post-test capabilities.

RECOMMENDED METHODOLOGIES

The following general methods obtained from *Standard Methods for the Examination of Water and Wastewater*, 18th Edition, American Public Health Association, Washington, DC 20005, are considered appropriate for establishing trends in the number of colony-forming units observed in the routine microbiological monitoring of ingredient water. It is recognized, however, that other combinations of media, time, and temperature of incubation may occasionally or even consistently result in higher numbers of colony-forming units being observed. The extended incubation periods that are usually required by some of the alternative methods available offer disadvantages that may outweigh the higher counts obtained. The somewhat higher baseline counts would not necessarily have greater utility in detecting an excursion or a trend.

Methodologies that can be recommended as generally satisfactory for monitoring pharmaceutical water systems are as follows:

Drinking Water:	POUR PLATE METHOD Minimum sample—1.0 mL Plate count agar Plate count agar 42 to 72 hours incubation at 30°C to 35°C
Purified Water:	POUR PLATE METHOD Minimum sample—1.0 mL Plate count agar 48 to 72 hours incubation at 30°C to 35°C
Water for Injection:	MEMBRANE FILTRATION METHOD Minimum sample—100 mL Plate count agar 48 to 72 hours incubation at 30°C to 35°C

Identification of Microorganisms

Identifying the isolates recovered from water monitoring methods may be important in instances where specific waterborne microorganisms may be detrimental to the products or processes in which the water is used. Microorganism information such as this may also be useful when identifying the source of microbial contamination in a product or process.

Often a limited group of microorganisms are continuously recovered from a water system. After repeated characterization, an experienced microbiologist may become proficient at their identification based on only a few traits such as colonial morphology and staining characteristics. This level of characterization is adequate for most situations.

Alert and Action Levels

The individual monographs for *Purified Water* and *Water for Injection* do not include specific microbial limits. These were purposefully omitted since most current microbiological techniques available require at least 48 hours to obtain definitive results. By that time, the water from which the sample was taken has already been employed in the production process. Failure to meet a compendial specification would require rejecting the product lot involved, and this is not the intent of an alert or action guideline. The establishment of quantitative microbiological guidelines for water for pharmaceutical purposes is in order because such guidelines will establish procedures that are to be implemented in the event that significant excursions beyond these limits occur.

Water systems should be microbiologically monitored to confirm that they continue to operate within their design specifications and produce water of acceptable quality. Monitoring data may be compared to established process parameters or product specifications. A refinement to the use of process parameters and product specifications is the establishment of Alert and Action Levels, which signal a shift in process performance. Alert and Action Levels are distinct from process parameters and product specifications in that they are used for monitoring and control rather than accept or reject decisions.

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~~**Alert Levels** are levels or ranges that, when exceeded, indicate that a process may have drifted from its normal operating condition. Alert Levels constitute a warning and do not necessarily require a corrective action.~~

~~**Action Levels** are levels or ranges that, when exceeded, indicate that a process has drifted from its normal operating range. Exceeding an Action Level indicates that corrective action should be taken to bring the process back into its normal operating range.~~

~~Alert and Action Levels are established within process and product specification tolerances and are based on a combination of technical and product related considerations. Consequently, exceeding an Alert or Action Level does not imply that product quality has been compromised.~~

~~Technical considerations used to establish Alert and Action Levels should include a review of equipment design specifications to ensure that the purification equipment is capable of achieving the required level of purity. In addition, samples should be collected and analyzed over a period of time to develop data reflecting normal water quality trends. Historical or statistically based levels can be established using the above data. Levels established in this way measure process performance and are independent of product concerns.~~

~~Product related Alert and Action Levels should represent both product quality concerns and the ability to effectively manage the purification process. These levels are typically based on a review of process data and an assessment of product sensitivity to chemical and microbiological contamination. The assessment of product susceptibility might include preservative efficacy, water activity, pH, etc. The levels should be set such that, when exceeded, product quality is not compromised.~~

~~Monitoring data should be analyzed on an ongoing basis to ensure that the process continues to perform within acceptable limits. An analysis of data trends is often used to evaluate process performance. This information can be used to predict departures from established operating parameters, thereby signaling the need for appropriate preventative maintenance.~~

~~It should be recognized that the microbial Alert and Action Levels established for any pharmaceutical water system are necessarily linked to the monitoring method chosen. Using the recommended methodologies, generally considered appropriate Action Levels are 500 colony forming units (cfu) per mL for *Drinking Water,* 100 cfu per mL for *Purified Water* and 10 cfu per 100 mL for *Water for Injection*.~~

~~It should be emphasized that the above action guidelines are not intended to be totally inclusive for every situation where ingredient waters are employed. For example, Gram negative microorganisms are not excluded from ingredient waters, nor is the presence of Gram negative microorganisms prohibited in *Drinking Water* in the Federal Regulations. The reason for this is that these microorganisms are ubiquitous to the aqueous environment and their exclusion would likely require a sterilization process that would not be appropriate or feasible in many manufacturing scenarios. However, there are situations where they might not be tolerated: in topical products and in some oral dosage forms. It is, therefore, incumbent upon the manufacturer to supplement the general action guidelines to fit each particular manufacturing situation.~~

■Water is widely used as a raw material, ingredient, and solvent in the processing, formulation, and manufacture of pharmaceutical substances and compendial articles. Its broad use makes it an important substance whose quality requires carefully established specifications to render it suitable for the majority of its uses. Because these varied uses each require tailored specifications, a number of compendial monographs have been created.

Control of the chemical purity of these waters is important and is the main purpose of the monographs in this compendium. Unlike other official articles, the bulk water monographs (*Purified Water* and *Water for Injection*) also limit how the article can be produced because of the belief that the nature and robustness of the purification process is directly related to the resulting purity. The chemical attributes listed in these monographs should be considered as a set of minimum specifications. More stringent specifications may be needed for some applications to ensure suitability for particular uses. Basic guidance on the appropriate applications of these waters is found in the monographs and is further explained in this chapter.

Control of the microbiological quality of water is important for many but not all of its uses. All packaged forms of water are required to be sterile either because their uses require this attribute or because potential contaminating microorganisms, if not removed or killed prior to packaging, could continue to grow unchecked to extremely high levels after packaging, rendering the water potentially unsuitable for many of its other nonsterile uses. USP has determined

that a microbial specification for the bulk monographed waters is inappropriate for several reasons. These waters can be used in a variety of applications, some requiring extreme microbiological control and others requiring none. Unlike for packaged waters, the needed microbial specification for a given bulk water depends upon its use. A single specification for this difficult-to-control attribute would unnecessarily burden some water users with irrelevant specifications and testing. However, other applications may require even more careful microbial control to avoid the proliferation of microorganisms ubiquitous to water during the purification, storage, and distribution of this substance. Another reason such a microbial specification would be inappropriate is related to the ''utility'' or continuous supply nature of this raw material. Microbial specifications are typically assessed by test methods that take at least 48 to 72 hours to generate results. Since pharmaceutical waters are generally produced by continuous processes and used in products and manufacturing processes soon after generation, the water is likely to have been used well before definitive test results are available. Failure to meet a compendial specification, whether relevant to that particular use or not, would require rejecting all product lots between the previous sampling's acceptable test result and a subsequent sampling's acceptable test result. However, the establishment of quantitative microbiological guidelines for specific pharmaceutical water uses is not totally inappropriate for especially critical uses. In these situations, manufacturing at risk (using the water in a continuous mode prior to availability of test results) may be contraindicated. Instead, action and alert levels should be used as in-process controls to keep the microbial quality of the water within levels that reflect a state of control of the water system with microbial counts well under any specification established for a specific critical use.

SOURCE/FEED WATER CONSIDERATIONS

To ensure adherence to certain minimal chemical and microbiological quality standards, water used in the production of drug substances or as source or feed water for the preparation of the various types of purified waters must meet the requirements of the National Primary Drinking Water Regulations (NPDWR) (40 CFR 141) issued by the U.S. Environmental Protection Agency (EPA) or comparable regulations for drinking water of the European Union or Japan. Limits on the types and quantities of certain organic and inorganic contaminants ensure that the water will contain only small quantities of potentially objectionable chemical species. Therefore, water pretreatment systems will only be challenged to remove small quantities of these potentially difficult-to-remove chemicals. Also, control of objectionable chemical contaminants at the source-water stage eliminates the need to specifically test for some of them (e.g., trihalomethanes and heavy metals) after the water has been further purified.

Microbiological requirements ensure the absence of coliforms, which, if determined to be of fecal origin, may indicate the potential presence of other potentially pathogenic microorganisms and viruses of fecal origin.

On the other hand, meeting these regulations does not rule out the presence of other microorganisms, which, while not considered a major public health concern could, if present, constitute a hazard or be considered undesirable in a drug substance or formulated product.

To accomplish microbial control, Municipal Water Authorities add to drinking water, among other things, disinfectants. Chlorine-containing and other oxidizing substances have been used for many decades for this purpose and have generally been considered, in and of themselves, to be relatively innocuous to humans. However, these oxidants can interact with naturally occurring organic matter to produce disinfection by-products (DBPs) such as trihalomethanes (THMs, including chloroform, bromodichloromethane, and dibromochloromethane) and haloacetic acids (HAAs, including dichloroacetic acid and trichloroacetic acid). The levels of DBPs produced vary with, among other things, the level and type of disinfectant used and the levels and types of organic materials found in the water. These may vary seasonally or even hourly.

High levels of DBPs are considered a health hazard, so control of their levels is mandated by Drinking Water Regulations intended to reduce exposure to these substances to nonhazardous levels. However, depending on the unit operations used for further water purification, a small fraction of the DBPs in the starting water may carry over to the finished water. Therefore, the importance of having minimal levels of DBPs in the starting water while achieving effective disinfection is important.

DBP levels in drinking water can be minimized by using disinfectants such as ozone, chloramines, or chlorine dioxide. Like chlorine, their oxidative properties are sufficient to damage some pretreatment unit operations and must be removed early in the pretreatment process. The complete removal of some of these disinfectants can be challenging. For example, chloramines may degrade during the disinfection process or during pretreatment removal, thereby releasing ammonia, which in turn can carry over to the finished water. Pretreatment unit operations must be designed and operated to adequately remove the disinfectant, drinking water DBPs, and objectionable disinfectant degradants. A serious problem can occur if unit operations designed to remove chlorine were, without warning, challenged with chloramine-containing drinking water from a municipality that had been mandated to cease use of chlorine disinfection to comply with ever tightening EPA Drinking Water THM specifications. Not only might the dechlorination process incompletely remove the chloramine (which could irreparably damage downstream unit operations), but the release of ammonia during this process might carry through pretreatment and prevent the finished water from passing compendial conductivity specifications. The purification process must be reassessed if the drinking water disinfectant is changed, emphasizing the need for a good working relationship and open communications between the pharmaceutical water manufacturer and the drinking water provider.

TYPES OF WATER

There are many different grades of water used for pharmaceutical purposes. Several of these water grades are described in *USP* monographs that specify uses, acceptable methods of preparation, and quality attributes. These waters

can be divided into two general types, bulk waters, which are typically produced on site where they are used, and packaged waters, which are produced, packaged, and sterilized to preserve microbial quality throughout their packaged shelf life. There are several specialized types of packaged waters, differing in their designated applications, packaging limitations, and other quality attributes.

There are also other types of water for which there are no monographs. These are all bulk waters, with names given for descriptive purposes only. Most of these waters are used in specific analytical methods. The associated text, created during an era predating USP's replacement of the archaic bulk water wet chemistry tests with tests for *Conductivity* and *Total Organic Carbon,* may or may not specify or imply certain quality attributes or modes of preparation. It is not the intent of USP that these nonmonographed waters necessarily adhere strictly to the stated or implied modes of preparation or attributes. Waters produced by other means or controlled by other test attributes may equally satisfy the intended uses for these waters. It is the user's responsibility to ensure that such waters, even if produced and controlled exactly as stated, be suitable for their intended use. Wherever the term "water" is used within this compendium without other descriptive adjectives or clauses, the intent is that water of no less purity than *Purified Water* be used.

What follows is a brief description of the various types of pharmaceutical waters and their significant uses or attributes. *Figure 1* may also be helpful in understanding some of the various types of waters.

BULK MONOGRAPHED WATERS

The following waters are typically produced in large volume by a multiple-unit operation water system and distributed by a piping system for use at the same site. These particular pharmaceutical waters must meet the quality attributes as specified in the related monographs, but the following discussion gives further insight as to their uses and requirements.

Purified Water—*Purified Water* (see *USP* monograph) is used as an excipient in the production of nonparenteral preparations and in other pharmaceutical applications, such as cleaning of certain equipment and nonparenteral product-contact components. Unless otherwise specified, *Purified Water* is also to be used for all tests and assays for which water is indicated (see *General Notices and Requirements*). *Purified Water* must meet the requirements for ionic and organic chemical purity and must be protected from microbial contamination. The minimal quality of source or feed water for the production of *Purified Water* is *Drinking Water.* This source water may be purified using unit operations that include deionization, distillation, ion exchange, reverse osmosis, filtration, or other suitable purification procedures. Purified water systems must be validated to reliably and consistently produce and distribute water of acceptable chemical and microbiological quality. Purified water systems that function under ambient conditions are particularly susceptible to the establishment of tenacious biofilms of microorganisms, which can be the source of undesirable levels of viable microorganisms or endotoxins in the effluent water. These systems require frequent sanitization and microbiological monitoring to ensure water of appropriate microbiological quality at the points of use.

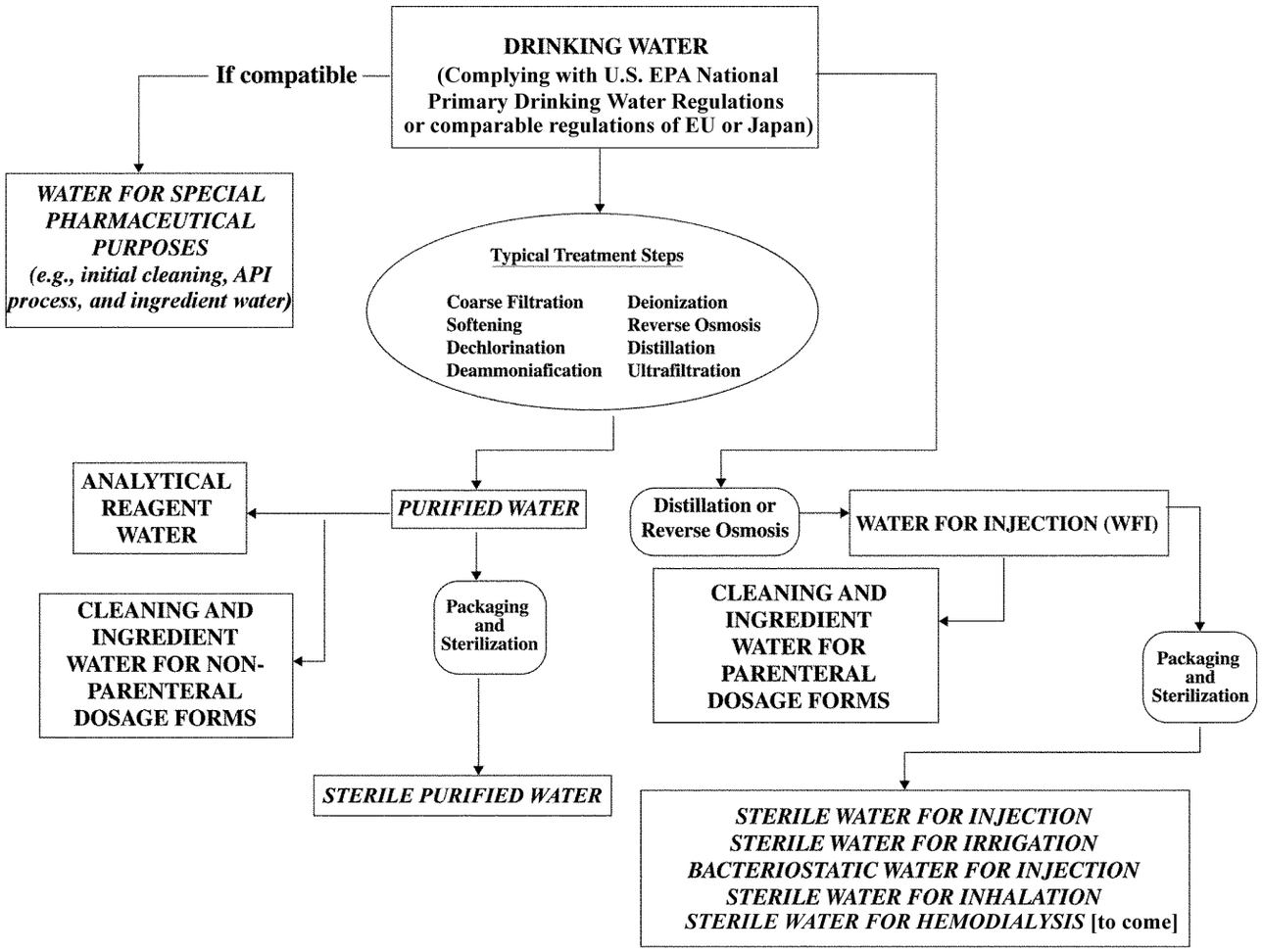


Fig. 1. Water for pharmaceutical purposes.

In-Process Revision

Water for Injection—*Water for Injection* (see *USP* monograph) is used as an excipient in the production of parenteral and other preparations where product endotoxin content must be controlled, and in other pharmaceutical applications, such as cleaning of certain equipment and parenteral product-contact components. The minimum quality of source or feed water for the generation of *Water for Injection* is *Drinking Water*. This source water may be preliminarily purified to render it suitable for subsequent distillation (or whatever other validated process is used according to the monograph). The resulting water must meet all of the chemical requirements for *Purified Water* as well as an additional bacterial endotoxin specification. Since endotoxins are produced by the kinds of microorganisms that are prone to inhabit water, the equipment and procedures used by the system to purify, store, and distribute *Water for Injection* must be designed to minimize or prevent microbial contamination as well as remove incoming endotoxin from the starting water. Water for injection systems must be validated to reliably and consistently produce and distribute this quality of water.

PACKAGED MONOGRAPHED WATERS

The following waters are packaged forms of either bulk *Purified Water* or bulk *Water for Injection* which have been sterilized to preserve their microbiological properties. These waters may have specific intended uses as indicated by their names and may also have restrictions on packaging configurations related to those uses. In general, these waters may be used in lieu of the bulk form of water from which they were derived. However, the user should take into consideration that the packaging and sterilization processes used for the articles may leach materials from the packaging material into the water over its shelf life, rendering it less pure than the original water placed into the package. The chemical attributes of these waters are still defined primarily by the wet chemistry methods and specifications similar to those formerly used for the bulk pharmaceutical waters prior to their replacement with conductivity and total organic carbon. It is the user's responsibility to ensure fitness for use of this article when used in manufacturing, clinical, or analytical applications where the purer bulk form of the water is indicated.

Sterile Purified Water—*Sterile Purified Water* (see *USP* monograph) is *Purified Water*, packaged and rendered sterile. It is used in the preparation of nonparenteral compendial dosage forms or in analytical applications requiring *Purified Water* where access to a validated *Purified Water* system is not practical, where only a relatively small quantity is needed, or where microbiologically controlled or sterile *Purified Water* is required.

Sterile Water for Injection—*Sterile Water for Injection* (see *USP* monograph) is *Water for Injection* packaged and rendered sterile. It is used for extemporaneous prescription compounding and as a sterile diluent for parenteral products. It may also be used for other applications where bulk *Water for Injection* or *Purified Water* is indicated but where assess to a validated water system is either not practical or only a relatively small quantity is needed. *Sterile Water for Injection* is packaged in single-dose containers not larger than 1 liter in size.

Bacteriostatic Water for Injection—*Bacteriostatic Water for Injection* (see *USP* monograph) is sterile *Water for Injection* to which has been added one or more suitable antimicrobial preservatives. It is intended to be used as a diluent in the preparation of parenteral products. It may be packaged in single-dose or multiple-dose containers not larger than 30 mL.

Sterile Water for Irrigation—*Sterile Water for Irrigation* (see *USP* monograph) is *Water for Injection* packaged and sterilized in single-dose containers of larger than 1 liter in size and intended to be delivered rapidly. It need not meet the requirement under small-volume injections in the general test chapter *Particulate Matter in Injections* ⟨788⟩. It may also be used in other applications where bulk *Water for Injection* or *Purified Water* is indicated but where access to a validated water system is not practical or where somewhat larger quantities than are provided as *Sterile Water for Injection* are needed.

Sterile Water for Inhalation—*Sterile Water for Inhalation* (see *USP* monograph) is *Water for Injection* that is packaged and rendered sterile and is intended for use in inhalators and in the preparation of inhalation solutions. It carries a less stringent specification for bacterial endotoxins than *Sterile Water for Injection*, so it is not suitable for parenteral applications.

Sterile Water for Hemodialysis—*Sterile Water for Hemodialysis* [*USP* monograph to come] is *Water for Injection* which has additional attributes for certain chemicals which have been shown to be problematic during hemodialysis. It is used for the dilution of hemodialysis concentrate and other hemodialysis applications.

NONMONOGRAPHED WATERS AND STEAM

Pharmaceutical Water—Cited in this chapter, this is a broad term referring to any water used in the preparation of active pharmaceutical ingredients, excipients, and finished products as well as any related process such as pharmaceutical equipment cleaning or product testing. The term covers a broad range of water purities, starting with the least pure allowed in any process for *USP* substances, *Drinking Water*, and extending to the highest purity reasonably achievable. The water's purity must be suitable for its intended use, but no less pure than the *USP* and cGMP requirements.

Drinking Water—Cited in *General Notices and Requirements*, the general test chapters, and the dietary supplement chapters, this water must comply with the quality attributes of the U.S. Environmental Protection Agency's National Primary Drinking Water Regulations (NPDWR) or comparable regulations of the European Union or Japan. It may be derived from a variety of sources including a public water utility, a private water supply (e.g., a well), or a combination of more than one of these sources. *Drinking Water* may be used in the early stages of cleaning pharmaceutical manufacturing equipment and product-contact components. *Drinking Water* is also the minimum quality of water which should be used for the preparation of official substances and other bulk pharmaceutical ingredients. Where required by the processing of the materials to achieve their required final purity, higher qualities of water may be needed, perhaps even as pure as *Water for Injection* or *Purified Water* Such higher purity waters might, however, receive only selected attributes to be of higher purity than *Drinking Water* (see *Water for Special Pharmaceutical Purposes* and *Endotoxin- and Microorganism-Controlled Water* below). *Drinking Water* is the prescribed source feed water for the production of pharmaceutical waters. As seasonal variations in the quality attributes of the *Drinking Water* supply can occur, due consideration to its synthetic and cleaning uses must be given. In addition, the processing steps in the production of pharmaceutical waters must be designed to accommodate this variability.

Potable Water—Cited in the *General Notices and Requirements*, the general test chapters, and the dietary supplement chapters, this is an older synonym for *Drinking Water* (derived from the French adjective *potable,* meaning drinkable).

NPDWR Water—Cited in this chapter, this water must comply with the U.S. Environmental Protection Agency's National Primary Drinking Water Regulations, the drinking water mandated for use in the United States. The specifications for this water, found in 40 CFR Part 141, include maximum contaminant levels for a large number of inorganic, organic, microbiological, and radioactive contaminants.

Water for Special Pharmaceutical Purposes—Cited in this chapter, this broad term is used to describe any type of water that does not have a monograph but has special purity requirements suited for its intended purposes.

Endotoxin- and Microorganism-Controlled Water—Cited in this chapter, this type of water has been subjected to conditions that control its microbial and endotoxin concentrations at a level suitable for its intended use. It may also have undergone some level of chemical purification.

LAL Reagent Water—Cited in the *USP* monographs as well as the general chapters, this is a water, usually *Water for Injection* which may have been sterilized and is free from a level of endotoxin that would yield any detectable reaction or interference with the Limulus Amebocyte Lysate reagent used in the *Bacterial Endotoxins Test* ⟨85⟩.

Endotoxin-Free Water—Cited in one *USP* monograph, this water is a synonymous with LAL Reagent Water.

Carbon Dioxide-Free Water—Cited in numerous *USP* monographs, general test chapters, and *NF* monographs, this is *Purified Water* or *Water for Injection* that has been prepared to remove dissolved carbon dioxide and bicarbonate during its purification and then either protected from carbon dioxide reabsorption during its preparation and storage or treated to drive off the dissolved carbon dioxide just prior to use, such as by sparging with an inert gas or by boiling. The *Reagents* section of *USP* describes its preparation as *Purified Water* that has been boiled for 5 minutes, cooled, and protected from atmospheric carbon dioxide adsorption. Practically speaking, it is extremely difficult to remove all carbon dioxide from the water by boiling or sparging, and if exposed to air at all, such as during cooling or when transferring a quantity of water to a working container for use in a test, readsorption is inevitable. Deionization by a mixed bed deionizer is an effective initial carbon dioxide removal approach. Distillation and reverse osmosis are less effective. Reintrusion of carbon dioxide is possible if the water is not properly protected after production. The usual uses of this type of water are for analyses requiring highly purified water or where the test is related to pH, acidity, or alkalinity and the concern is that the carbon dioxide in the water could affect the test result. The efficacy of the carbon dioxide limitation process should be evaluated for its impact on the tests in which the water is used. Normally, the small amount absorbed during reasonably rapid, open-to-the-air handling of truly carbon dioxide-free water will not affect the testing where *Carbon Dioxide-Free Water* is indicated.

Ammonia-Free Water—Cited in only one *USP* monograph, this is *Purified Water* or *Water for Injection* that has been produced in such a way as to prevent the carryover of ammonia from the source water. Ammonia is typically only a problem in regions where chloramines are used as the *Drinking Water* disinfectant. Deionization by a mixed bed deionizer is very effective at removing ammonia, but distillation and reverse osmosis are less effective. In order for distillation and reverse osmosis to produce *Ammonia-Free Water* in chloramine-using regions, the ammonia must be removed by earlier unit operations prior to entering the distillation or reverse osmosis units. The use of this water is for a test related to pH and the concern, like with carbon dioxide, is that the pH of the water may affect the test result. In most laboratory settings, there is insufficient atmospheric ammonia to create a need for ammonia reintrusion protection, unlike the analogous protection that would be needed for *Carbon Dioxide-Free Water.*

High Purity Water—Cited in one *USP* monograph and one general chapter, this water is well characterized in the general test chapter *Containers* ⟨661⟩ . In essence, it is water that is prepared by several sequential steps, an interim one of which is distillation, that renders it extremely pure relative to on-line conductivity, particulates, and copper content. This water is used for many of the reagents and tests for containers in ⟨661⟩ where less pure waters would not perform acceptably, as well as for the reagents employed where cited for the *USP* monograph tests.

Distilled Water—Cited in several *USP* monographs and general test chapters, this water is, as the name suggests, produced by vaporizing liquid water and condensing it in a purer state. This water is used primarily for reagent preparation in the *USP* monographs where pure water is needed and in the general test chapter primarily for cleaning purposes where the leaving of no water impurity residuals is important. It is also cited as the starting water used for making *High Purity Water.*

Freshly Distilled Water—Cited in only one *USP* monograph, this water is prepared in a similar fashion to *Distilled Water,* though as the name suggests, immediately before use. It is used for preparing standards and control solutions

for injection into test animals. Because of this use and the term "freshly", the implied attributes are its chemical purity as well as its low endotoxin and bioburden (though no reference to these microbial attributes or specific protection from recontamination is mentioned). Due to the nature of the testing, *Water for Injection* could be a reasonable substitute, though as for any test, the suitability of the water must be verified for this use.

Deionized Water—Cited in numerous *USP* monographs, general test chapters, and dietary supplement monographs, this water is produced by an ion exchange process in which the contaminating ions are replaced with either H^+ or OH^- ions. In the *USP* monographs and general test chapters, this water is indicated for cleaning and reagent preparation purposes. In one general test chapter, it is listed as a suitable substitute for *Purified Water* In the dietary supplement monographs, it is listed as the water to be used wherever "water" is mentioned, which includes reagent and article preparations as well as for cleaning. Due to the nature of the testing, *Purified Water* could be a reasonable substitute, though as for any test, the suitability of the water must be verified for these uses.

Freshly Deionized Water—Cited in only two related *USP* monographs, this water is prepared in a similar fashion to *Deionized Water,* though as the name suggests, immediately before it is to be used. This implies the need to avoid any adventitious contamination from the air or container leachables, which in turn implies a reasonably high degree of purity. This water is indicated for use wherever "water" is mentioned, which includes reagent and article preparations as well as for cleaning. Due to the nature of the testing, *Purified Water* could be a reasonable substitute for most of the applications mentioned, though as for any test, the suitability of the water must be verified for these uses, particularly for its indicated use in preparing mobile phase solutions where highly deionized water is needed.

Deionized Distilled Water—Cited in only two *USP* monographs, this water is produced by deionizing (see *Deionized Water* above) *Distilled Water* (also see above). This water is used as a reagent in a chromatography test that requires a high purity. Because of the importance of this high purity, water that barely meets the requirements for *Purified Water* would not be acceptable.

Deaerated Water—Cited in two *USP* monographs and two general information chapters, this water is *Purified Water* that has been treated to reduce the content of dissolved air by any suitable means such as by reducing the headspace air pressure in a closed container, boiling for at least five minutes, or sonication. The *Reagents* section of *USP* also describes its preparation. *Deaerated Water* is primarily indicated for use in dissolution testing where the presence of high levels of dissolved gases could outgas during the test and interfere with the test results or accurate volumetric withdrawals.

Clean Steam—Clean Steam (also commonly known as Pure Steam or Additive-Free Steam) is not specifically cited in *USP,* but is commonly used throughout the pharmaceutical industry. Its quality is sometimes confusingly identified in various references by either the quality of the water from which it is produced or by the quality of the condensate formed from it, both of which make reference to a *USP* monographed bulk water. Though these various preparation and end-quality definitions may serve their respective purposes in isolation, their inconsistently assigned descriptive names create confusion when taken out of context. Therefore, the purpose of this discussion is to clarify the term "Clean Steam," its production, uses, and quality. Clean Steam may be prepared analogously to either *Purified Water*

or *Water for Injection* but vaporized and distributed in such a fashion as to render its condensate equivalent in quality to that of *Water for Injection* It is used where its condensate directly contacts product or product contact surfaces such as during cleaning or sterilization of products, product components, and other product contact surfaces and where there is no subsequent processing step to remove any codeposited impurity residues. The primary intent of using this quality of steam is to ensure that articles or product contact surfaces exposed to it are not contaminated by residues that may be deposited by the steam. The source of this contamination could originate from entrained source water, steam additives, or the steam production and distribution system itself. Depending on its use in sterilization, such as for porous autoclave loads and SIP systems, the presence of even small quantities of noncondensable gases or an unsaturated or dry state, such as would exist in a superheated condition, could compromise the steam's sterilizing properties. Therefore, control of these attributes may also be necessary.

VALIDATION AND QUALIFICATION OF WATER PURIFICATION, STORAGE, AND DISTRIBUTION SYSTEMS

Establishing the dependability of pharmaceutical water purification, storage, and distribution systems requires an appropriate period of monitoring and observation. Ordinarily, few problems are encountered in maintaining the chemical purity of *Purified Water* and *Water for Injection* Nevertheless, the advent of using conductivity and TOC to define chemical purity has allowed the user to more quantitatively assess the water's chemical purity and its variability as a function of routine pretreatment system maintenance, regeneration, etc. Even the presence of such unit operations as heat exchangers and use point hoses can compromise the chemical quality in an otherwise well-controlled water system. Therefore, an assessment of the consistency of the water's chemical purity over time must be part of the validation program. However, even with the most well controlled chemical quality, it is often more difficult to consistently meet established microbiological quality criteria owing to phenomena occurring during and after chemical purification. A typical program involves intensive daily sampling and testing of major process points for at least one month after operational criteria have been established for each unit operation, point of use, and sampling point.

Validation is the process whereby substantiation to a high level of assurance that a specific process will consistently produce a product conforming to an established set of quality attributes is acquired and documented. Prior to and during the very early stages of validation, the critical process parameters and their operating ranges are established. A validation program qualifies the design, installation, operation, and performance of equipment. It begins when the system is defined and moves through several stages, installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ). A graphical representation of a typical water system validation life cycle is shown in *Figure 2.*

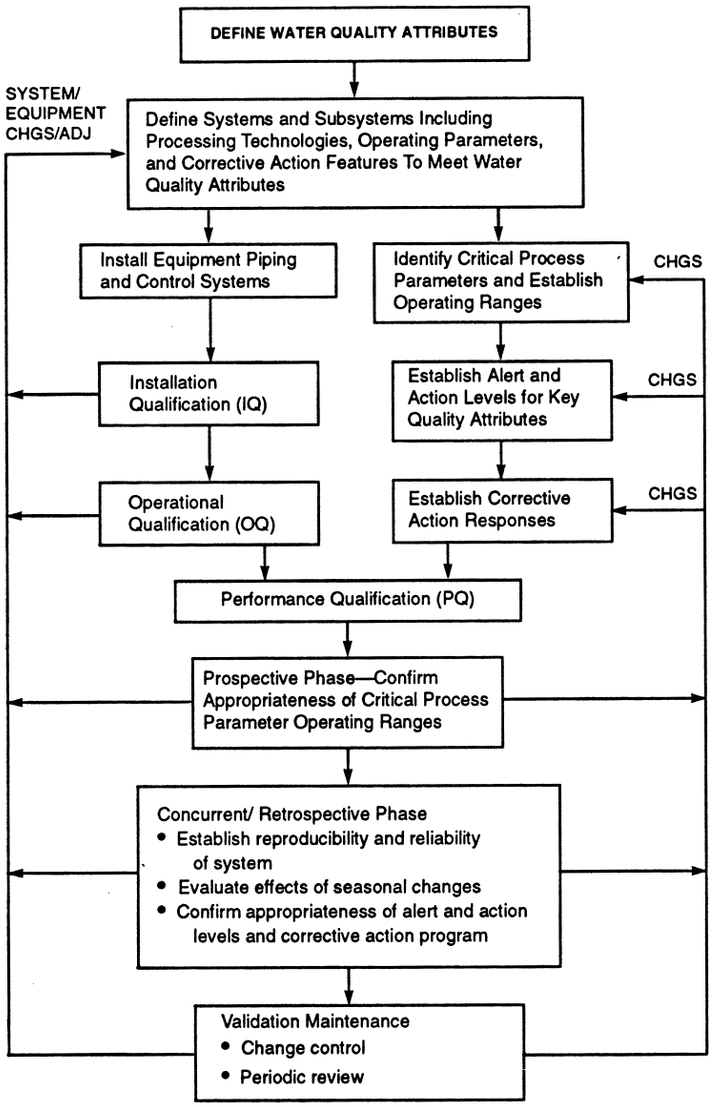


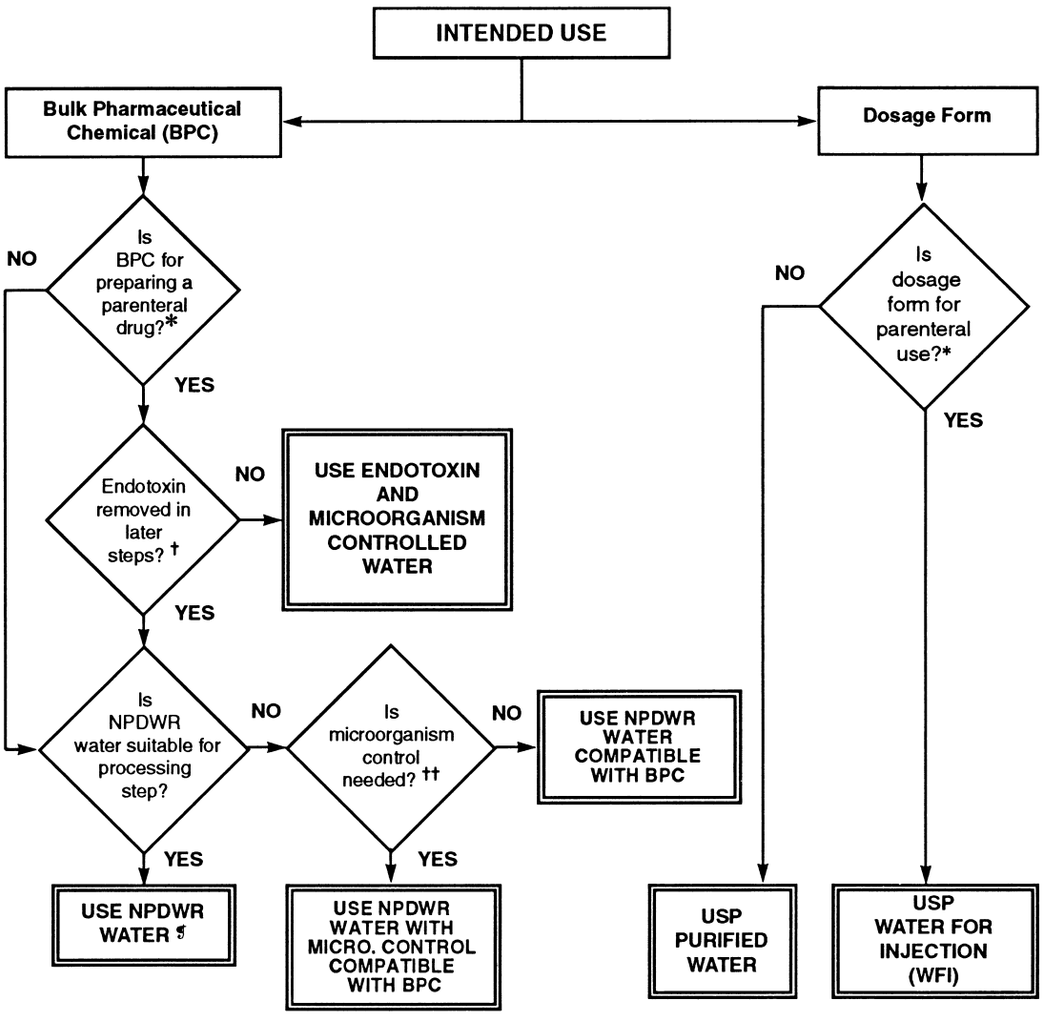
Fig. 2. Water system validation life cycle.

A validation plan for a water system typically includes the following steps: (1) establishing standards for quality attributes and operating parameters; (2) defining systems and suitable subsystems to produce the desired quality attributes from the available source water; (3) selecting equipment, controls, and monitoring technologies; (4) developing an IQ stage consisting of instrument calibrations, inspections to verify that the drawings accurately depict the as-built configuration of the water system and, where necessary, special tests to verify that the installation meets the design requirements; (5) developing an OQ stage consisting of tests and inspections to verify that the equipment, system alerts, and controls are operating reliably and that appropriate Alert and Action Levels are established (this phase of qualification may overlap with aspects of the next step); and (6) developing a prospective PQ stage to confirm the appropriateness of critical process parameter operating

ranges (During this phase of validation, *alert and action levels* for key quality attributes and operating parameters are verified.); (7) supplementing a validation maintenance program (also called continuous validation life cycle) that includes a mechanism to control changes to the water system and establishes and carries out scheduled preventive maintenance including recalibration of instruments (In addition, validation maintenance includes a monitoring program for critical process parameters and a corrective action program.); (8) instituting a schedule for periodic review of the system performance and requalification; and (9) completing protocols and documenting Steps 1 through 8.

PURIFIED WATER AND WATER FOR INJECTION SYSTEMS

The design, installation, and operation of systems to produce *Purified Water* and *Water for Injection* include similar components, control techniques, and procedures. The quality attributes of both waters differ only in the presence of a bacterial endotoxin requirement for *Water for Injection* and in their methods of preparation, at least at the last stage of preparation. The similarities in the quality attributes provide considerable common ground in the design of water systems to meet either requirement. The critical difference is the degree of control of the system and the final purification steps needed to ensure bacterial and bacterial endotoxin removal. Production of pharmaceutical water employs sequential unit operations (processing steps) that address specific water quality attributes and protect the operation of subsequent treatment steps as shown in *Figure 2*. A typical evaluation process to select an appropriate water quality for a particular pharmaceutical purpose is shown in the decision tree in *Figure 3.* These diagrams may be used to assist in defining requirements for specific water uses and in the selection of unit operations. The final unit operations used to produce *Water for Injection* have been limited to distillation and reverse osmosis. Distillation has a long history of reliable performance and can be validated as a unit operation for the production of *Water for Injection.* Other technologies such as ultrafiltration may be suitable in the production of *Water for Injection* but at this time experience with this process is not widespread.



* Water for sterile BPC's or dosage forms must be rendered sterile if there is not a sterilization step following addition.

† Endotoxin removal can occur either in water treatment or in BPC process.

†† Microorganism control can occur either in water treatment or in BPC process.

¶ NPDWR Water—Water meeting EPA national primary drinking water regulations.

Fig. 3. Selection of water for pharmaceutical purposes.

The validation plan should be designed to establish the suitability of the system and to provide a thorough understanding of the purification mechanism, range of operating conditions, required pretreatment, and the most likely modes of failure. It is also necessary to demonstrate the effectiveness of the monitoring scheme and to establish the requirements for validation maintenance. Trials conducted in a pilot installation can be valuable in defining the operating parameters and the expected water quality and in identifying failure modes. However, qualification of the specific unit operation can only be performed as part of the validation of the installed operational system. The selection of specific unit operations and design characteristics for a

water system should take into account the quality of the feed water, the technology chosen for subsequent processing steps, the extent and complexity of the water distribution system, and the appropriate compendial requirements. For example, in the design of a system for *Water for Injection*, the final process (distillation or reverse osmosis) must have effective bacterial endotoxin reduction capability and must be validated.

UNIT OPERATIONS CONCERNS

The following is a brief description of selected unit operations and the operation and validation concerns associated with them. This review is not comprehensive in that not all unit operations are discussed, nor are all potential problems addressed. The purpose is to highlight issues that focus on the design, installation, operation, maintenance, and monitoring parameters that facilitate water system validation.

Prefiltration

Filtration technology plays an important role in water systems, and filtration units are available in a wide range of designs and for various applications. Removal efficiencies differ significantly from coarse filters, such as multimedia or sand for larger water systems and depth cartridges for smaller water systems, to membrane filters for very small particle control. Unit and system configurations vary widely in type of filtering media and location in the process. (The use of membrane filters is discussed in a later paragraph.) Granular or cartridge filters are used for prefiltration and are often situated at or near the head of the water pretreatment system prior to unit operations designed to remove the source water disinfectants. This location, however, does not preclude the need for periodic microbial control since biofilm can still proliferate in the presence of source water disinfectants, albeit slower than in their absence. These prefilters remove solid contaminants down to a size of 7 to 10 μm from the water supply and protect downstream system components from particulates that can inhibit equipment performance and shorten their effective life. Design and operational issues that may impact performance of depth filters include channeling of the filtering media, blockage from silt, microbial growth, and filtering-media loss during improper backwashing. Control measures include pressure and flow monitoring during use and backwashing, sanitizing, and replacing filtering media. An important design concern is sizing of the filter to prevent channeling or media loss resulting from inappropriate water flow rates as well as proper sizing to minimize excessive frequent or infrequent backwashing or cartridge filter replacement.

Activated Carbon

Activated carbon beds adsorb low molecular weight organic material and oxidizing additives, such as chlorine and chloramine compounds, removing them from the water. They are used to achieve certain quality attributes and to protect against reaction with downstream stainless steel surfaces, resins, and membranes. The chief operating concerns regarding activated carbon beds include the propensity to support bacteria growth, the potential for hydraulic channeling, the inability to be regenerated in situ, and the shedding of bacteria, endotoxins, organic chemicals, and fine carbon particles. Control measures include appropriate high water flow rates, sanitization with hot water or steam, backwashing, testing for adsorption capacity, and frequent replacement of the carbon bed. It is important to note that the use of steam for carbon bed sanitization is often incompletely effective due to channeling rather than even permeation through the bed. This phenomenon can usually be avoided by using hot water sanitization. Alternative technologies to

activated carbon beds can be used in order to avoid their microbial problems, such as disinfectant-neutralizing chemical additives and regenerable organic scavenging devices. However, these alternatives do not function by the same mechanisms as activated carbon, may not be as effective at removing some organics, and have a different set of operating concerns and control measures that may be nearly as troublesome as activated carbon beds.

Additives

Chemical additives are used in water systems (a) to control microorganisms by use of sanitants such as chlorine compounds and ozone, (b) to enhance the removal of suspended solids by use of flocculating agents, (c) to remove chlorine compounds, (d) to avoid scaling on reverse osmosis membranes, and (e) to adjust pH for more effective removal of carbonate and ammonia compounds by reverse osmosis. These additives do not constitute ''added substances'' so long as they are either removed by subsequent processing steps or they naturally and completely autodegrade or equilibrate to ions and molecules native to the water such as hydrogen and hydroxide ions, oxygen, or water itself. Control of additives to ensure a continuously effective concentration and subsequent monitoring to ensure their removal as well as their non-native reaction/degradation products should be designed into the system and included in the monitoring program.

Organic Scavengers

Organic scavenging devices use macroreticular weakly basic anion-exchange resins capable of removing organic material and endotoxins from the water. They can be regenerated with appropriate biocidal caustic brine solutions. Operating concerns are associated with organic scavenging capacity, particulate, chemical and microbiological fouling of the reactive resin surface, flow rate, regeneration frequency, and shedding of resin fragments. Control measures include testing of effluent, backwashing, monitoring hydraulic performance, and using downstream filters to remove resin fines.

Softeners

Water softeners may be located either upstream or downstream of disinfectant removal units. They utilize sodium-based cation exchange resins to remove water-hardness ions, such as calcium and magnesium, that could foul or interfere with the performance of downstream processing equipment such as reverse osmosis membranes, deionization devices, and distillation units. Water softeners can also be used to remove other lower affinity cations, such as the ammonium ion, that may be released from chloramine disinfectants commonly used in drinking water and which might otherwise carryover through other downstream unit operations. If ammonium removal is one of its purposes, the softener must be located downstream of the disinfectant removal operation, which itself may liberate ammonium from neutralized chloramine disinfectants. Water softener resin beds are regenerated with concentrated sodium chloride solution (brine). Concerns include microorganism proliferation, channeling, appropriate water flow rates and contact time, ion-exchange capacity, organic and particulate resin fouling, fracture of the resin beads, resin degradation by excessively chlorinated water, and contamination from the brine solution used for regeneration. Control measures include recirculation of water during periods of low water use, periodic sanitization of the resin and brine system, use of microbial control devices (e.g., ultraviolet and chlorine), locating the unit upstream of the disinfectant removal step (if used only for softening), appropriate regeneration frequency, effluent chemical monitoring (e.g., hardness ions

and possibly ammonium), and downstream filtration to remove resin fines. If a softener is used for ammonium removal from chloramine-containing source water, then capacity, contact time, resin surface fouling, pH, and regeneration frequency are very important.

Deionization

Deionization (DI), electrodeionization (EDI), and continuous deionization (CDI) are effective methods of improving the chemical quality attributes of water by removing cations and anions. DI systems have charged resins that require periodic regeneration with an acid and base. Typically, cationic resins are regenerated with either hydrochloric or sulfuric acid, which replace the captured positive ions with hydrogen ions. Anionic resins are regenerated with sodium or potassium hydroxide, which replace captured negative ions with hydroxide ions. Both regenerant chemicals are biocidal and offer a measure of microbial control. The system can be designed so that the cation and anion resins are in separate or ''twin'' beds or they can be mixed together to form a mixed bed. Twin beds are easily regenerated but deionize water less efficiently than mixed beds, which have a considerably more complex regeneration process. Rechargeable resin canisters can also be used for this purpose.

The EDI and CDI systems use a combination of mixed resin, selectively permeable membranes, and an electric charge, providing continuous flow (product and waste concentrate) and continuous regeneration. Water enters both the resin section and the waste (concentrate) section. As it passes through the resin, it is deionized to become product water. The resin acts as a conductor enabling the electrical potential to drive the captured cations and anions through the resin and appropriate membranes for concentration and removal in the waste water stream. The electrical potential also separates the water in the resin (product) section into hydrogen and hydroxide ions. This permits continuous regeneration of the resin without the need for regenerant additives. However, unlike conventional deionization, EDI and CDI units must start with water that is already pretreated to be fairly pure because they cannot handle the heavier ion load of unpurified source water.

Concerns for all forms of deionization units include microbial and endotoxin control, chemical additive impact on resins and membranes, and loss, degradation, and fouling of resin. Issues of concern specific to DI units include regeneration frequency, channeling, organic leaching from new resins, complete resin separation for mixed bed regeneration, and mixing air contamination (mixed beds). Control measures vary but typically include recirculation loops, effluent microbial control by ultraviolet light, conductivity monitoring, resin testing, microporous filtration of mixing air, microbial monitoring, frequent regeneration to minimize and control microorganism growth, sizing the equipment for suitable water flow and contact time, and use of elevated temperatures. Internal distributor and regeneration piping for mixed bed units should be configured to ensure that regeneration chemicals contact all internal bed and piping surfaces and resins. Rechargeable canisters can be the source of contamination and should be carefully monitored. Full knowledge of previous resin use, minimum storage time between regeneration and use, and appropriate sanitizing procedures are critical factors ensuring proper performance.

Reverse Osmosis

Reverse osmosis (RO) units employ a semipermeable membrane and a substantial pressure differential to drive water through the membrane to achieve chemical, microbial, and endotoxin quality improvement. The process streams consist of supply water, product water (permeate), and wastewater (reject). Pretreatment and system configuration

variations and chemical additives may be necessary depending on source water to achieve desired performance and reliability. Concerns associated with the design and operation of RO units include membrane materials that are extremely sensitive to sanitizing agents; to particulate, chemical, and microbial membrane fouling; to membrane and seal integrity; to the passage of dissolved gases, such as carbon dioxide and ammonia; and to the volume of wastewater. Failure of membrane or seal integrity will result in product water contamination. Methods of control consist of suitable pretreatment of the water stream, appropriate membrane material selection, integrity challenges, membrane design and heat tolerance, periodic sanitization, and monitoring of differential pressures, conductivity, microbial levels, and total organic carbon. The configuration of the RO unit offers control opportunities by expanding the single pass scheme to parallel staged, reject staged, two-pass, and combination designs. An example would be the use of a two-pass design to improve reliability, quality, and efficiency. The development of RO units that can tolerate sanitizing water temperatures as well as operate efficiently at elevated temperatures has added greatly to their microbial control and to the avoidance of biofouling. RO units can be used alone or in combination with DI and EDI units for operational and quality enhancements.

Ultrafiltration

Ultrafiltration is another technology that uses a permeable membrane, but unlike RO, it works by mechanical separation rather than osmosis. Due to the ability of the membrane to sieve out macromolecules (typically greater than about 20 K daltons) depending on pore size and other factors, macromolecular and microbial impurities, such as endotoxins, can be retained by these membranes, effectively removing them from the effluent. This technology may be appropriate as an intermediate or final purification step. Similar to RO, successful performance is dependent upon pretreatment of the water by upstream unit operations. Issues of concern include compatibility of membrane material with heat and sanitizing agents, membrane integrity, fouling by particles and microorganisms, and seal integrity. Control measures include filtration medium selection, sanitization, tangential flow designs capable of flushing the membrane surface, integrity challenges, regular cartridge changes, elevated feed water temperature, and monitoring total organic carbon and differential pressure. Additional flexibility in operation is possible based on the way units are arranged such as in a parallel or series configuration. Care should be taken to avoid stagnant water conditions that could promote microorganism growth in back-up or standby units.

Microporous/Microbial Retentive Filtration

Microbial retentive membrane filters have a larger effective pore size than ultrafilters and are used to prevent the passage of microorganisms and similarly sized particles. Filters are rated by their manufacturer for the theoretical smallest size of bacterial cell they are capable of retaining. The generally accepted rating considered to retain all bacteria from a gas stream is 0.2 or 0.22 µm (absolute, not nominal rating). When used on air or gas vents for tanks and other unit operations, as well as for compressed air gases used in the regeneration of mixed bed deionization units, the membrane surface is typically hydrophobic (nonwettable by water). Areas of concern are blockage of tank vents by condensed water vapor or trapped particulate matter, which can cause mechanical damage to the tank, and concentration of microorganisms on the surface of the membrane filter, creating the potential for contamination of the tank or deionizer contents. Control measures include heat tracing and proper orientation of vent filter housings to prevent accumu-

lation of vapor condensate. Sterilization of the unit prior to initial use, and periodically thereafter, as well as regular filter changes are recommended control methods.

Microbial retentive filters are also sometimes used for water filtration in the purification systems or in distribution piping. Though microbial retentive filters, treated to be hydrophilic and having an absolute filter rating of 0.2 or 0.22 µm, are considered to be sterilizing filters for process streams and product formulations, their use in water systems should either be avoided or very carefully controlled because these units can become a source for microbial contamination. The potential exists for the release of microorganisms should the membrane filter rupture or as a result of microbial grow-through. There is also evidence that the kinds of microorganisms that proliferate in ambient water systems are of a size and possess cell surface properties that could allow their passage through these filters. Filters of smaller retention ratings (e.g., 0.1 µm) may be necessary to more definitively retain these aquatic microorganisms.

Filters that are intended to be microretentive should be sanitized and integrity tested prior to initial use and at appropriate intervals thereafter. It may also be necessary to frequently replace these filters to avoid grow-through as well as release of endotoxin from the accumulated bioburden on the upstream side of the filters. As an added measure of protection, in-line ultraviolet lamps, appropriately sized for the flow rate, may be used just upstream of microretentive filters to inactivate microorganisms prior to their capture by the filter to avoid or greatly delay filter grow-through.

Microretentive filters may be used downstream of unit operations that tend to release microorganisms or upstream of unit operations that are sensitive to microorganisms. Microretentive filters may also be used to filter water feeding the distribution system. Concerns include flow rate, membrane and seal integrity, retention capacity, and service duration. Control measures include monitoring differential pressure and endotoxin levels, proper sizing, membrane integrity testing, placing ultraviolet lamps immediately upstream, and configuring units in series to control break-through.

These hydrophilic filters can also be treated to have a positive charge on the surface of the filter media. Such charged filters can additionally be used to reduce endotoxin levels in the fluids passing through them by electrostatic attraction and adsorption. However, such applications are difficult to validate for endotoxin retention because their endotoxin retention capacity for "natural" endotoxin is difficult to gauge from purified endotoxin retention and because the amount of endotoxin in the water, or pyroburden, can be quite variable. These factors make usage duration difficult to validate.

Ultraviolet Light

The use of ultraviolet (UV) light for microbial control is discussed under the *Sanitization* heading, but its applications to chemical purification are also emerging. At wavelengths of 185 nm, UV light has demonstrated utility in the destruction of the chlorine containing disinfectants used in source water as well as for interim stages of water pretreatment. This wavelength of UV light has also been used to reduce TOC levels in recirculating distribution systems. Areas of concern include adequate UV intensity and residence time, unforeseen hyperchlorination of the source water overwhelming the photodegradation capability, release of ammonia from the photodegradation of chloramines, and unapparent UV bulb failure.

Distillation

Distillation units provide chemical and microbial purification via thermal vaporization, mist elimination, and water vapor condensation. A variety of designs are available in-

cluding single effect, multiple effect, and vapor compression. The latter two configurations are normally used in larger systems because of their generating capacity and efficiency. Distilled water systems may require less rigorous control of feed water quality than do membrane systems. Areas of concern include carry-over of gaseous impurities such as ammonia and carbon dioxide, faulty mist elimination, evaporator flooding, inadequate blowdown, stagnant water in condensers and evaporators, pump and compressor seal design, pinhole evaporator and condenser leaks, and conductivity (quality) variations during start-up and operation.

Methods of control consist of preliminary decarbonation steps, reliable mist elimination, visual or automated high water level indication, use of sanitary pumps and compressors, proper drainage during inactive periods, blow down control, on-line conductivity sensing with automated diversion of unacceptable quality water to the waste stream, and periodic integrity testing for pinhole leaks.

Storage Tanks

Storage tanks are included in water distribution systems to optimize processing equipment capacity. Storage also allows for routine maintenance while maintaining continuous supply to meet manufacturing needs. Design and operation considerations are needed to prevent or minimize the development of biofilm, to minimize corrosion, to aid in the use of chemical sanitization of the tanks, and to safeguard mechanical integrity. These considerations may include using closed tanks with smooth interiors and the ability to spray the tank headspace. This minimizes corrosion and biofilm development and aids in thermal and chemical sanitization. Storage tanks require venting to compensate for the dynamics of changing water levels. This can be accomplished with a hydrophobic microbial retentive membrane filter fitted onto an atmospheric vent. Alternatively, an automatic membrane-filtered compressed gas pressurization and venting system may be used. In both cases, rupture disks equipped with a rupture alarm device should be used as a further safeguard for the mechanical integrity of the tank. Areas of concern include microbial growth or corrosion due to nonuniform sanitization and microbial contamination from unapparent nonalarmed rupture disk failures that are caused by condensate occlusion of hydrophobic vent filters.

Distribution Systems

Distribution system configuration should allow for either the continuous flow of water in the piping by means of recirculation or should provide for the periodic flushing of nonrecirculating, dead-end, or one-way systems. Experience has shown that continuously recirculated systems are easier to maintain. Pumps should be designed to deliver fully turbulent flow conditions to facilitate thorough heat distribution (for hot water sanitized systems) as well as thorough chemical sanitant distribution. Pumps also appear to either retard the development of biofilms or force its development to be less susceptible to shearing into the water.

Components and distribution lines should be sloped and fitted with drain points so that the system can be completely drained. In stainless steel distribution systems where the water is circulated at a high temperature, dead legs and low-flow conditions should be avoided, and valved tie-in points should have length-to-diameter ratios of 6 or less. If constructed of heat tolerant plastic, this ratio should be even less to avoid cool points where biofilm development could occur. In ambient temperature distribution systems, particular care should be exercised to avoid or minimize dead legs of any length and provide for complete drainage. If the system is intended to be steam sanitized, careful sloping and low-point drainage is crucial to sanitization success.

If system drainage is intended as a microbial control strategy, it should also be configured to be dried by passage of dry compressed air or nitrogen throughout the system because drained moist piping will also support microbial proliferation. Water exiting from the distribution system should not be returned to the system.

The distribution design should include the placement of sampling valves in the storage tank and at other locations, such as in the return line of the recirculating water system. Where feasible, the primary sampling sites for water should be the valves that deliver water to the points of use. Direct connections to processes or auxiliary equipment should be designed to prevent reverse flow into the controlled water system. Hoses and heat exchangers that are attached to points of use in order to deliver water for a particular use must not degrade the water quality chemically or microbiologically. The distribution system should permit sanitization for microorganism control. The system may be continuously operated at sanitizing conditions or sanitized periodically.

INSTALLATION, MATERIALS OF CONSTRUCTION, AND COMPONENT SELECTION

Installation techniques are important because they can affect the mechanical, corrosive, and sanitary integrity of the system. Valve installation attitude should promote gravity drainage. Pipe supports should provide appropriate slopes for drainage and should be designed to support the piping adequately under worst-case thermal conditions. The methods of connecting system components including units of operation, tanks, and distribution piping require careful attention to preclude potential problems. Stainless steel welds should provide reliable joints that are internally smooth and corrosion-free. Low carbon stainless steel, compatible wire filler, where necessary, inert gas, automatic welding machines, and regular inspection and documentation help to ensure acceptable weld quality. Follow-up cleaning and passivation are important for removing contamination and corrosion products and to re-establish the passive corrosion resistant surface. Plastic materials can be fused (welded) in some cases and also require smooth, uniform internal surfaces. Adhesives should be avoided due to the potential for voids and chemical reactions. Mechanical methods of joining, such as flange fittings, require care to avoid the creation of offsets, gaps, penetrations, and voids. Control measures include good alignment, properly sized gaskets, appropriate spacing, uniform sealing force, and the avoidance of threaded fittings.

Materials of construction should be selected to be compatible with control measures such as sanitizing, cleaning, and passivating. Temperature rating is a critical factor in choosing appropriate materials because surfaces may be required to handle elevated operating and sanitization temperatures. Should chemicals or additives be used to clean, control, or sanitize the system, materials resistant to these chemicals or additives must be utilized. Materials should be capable of handling turbulent flow and elevated velocities without wear of the corrosion-resistant film such as the passive chromium oxide surface of stainless steel. The finish on metallic materials such as stainless steel, whether it is a refined mill finish, polished to a specific grit, or an electropolished treatment, should complement system design and provide satisfactory corrosion and microbial activity resistance as well as chemical sanitizability. Auxiliary equipment and fittings that require seals, gaskets, diaphragms, filter media, and membranes should exclude materials that permit the possibility of extractables, shedding, and microbial activity. Insulating materials exposed to stainless steel surfaces should be free of chlorides to avoid the phenomenon of stress corrosion cracking that can lead to system contamination and the destruction of tanks and critical system components.

Specifications are important to ensure proper selection of materials and to serve as a reference for system qualification and maintenance. Information such as mill reports for stainless steel and reports of composition, ratings, and material handling capabilities for nonmetallic substances should be reviewed for suitability and retained for reference. Component (auxiliary equipment) selection should be made with assurance that it does not create a source of contamination intrusion. Heat exchangers should be double tube sheet or concentric tube design. They should include differential pressure monitoring or utilize heat transfer medium of equal or better quality to avoid problems should leaks develop. Pumps should be of sanitary design with seals that prevent contamination of the water. Valves should have smooth internal surfaces with the seat and closing device exposed to the flushing action of water, such as occurs in diaphragm valves. Valves with pocket areas or closing devices (e.g., ball, plug, gate, globe) that move into and out of the flow area should be avoided.

SANITIZATION

Microbial control in water systems is achieved primarily through sanitization practices. Systems can be sanitized using either thermal or chemical means. Thermal approaches to system sanitization include periodic or continuously circulating hot water and the use of steam. These techniques are limited to systems that are compatible with the higher temperatures needed to achieve sanitization, such as stainless steel and some polymer formulations. Although thermal methods control biofilm development, they are not effective in removing established biofilms that could become a nutrient source for rapid biofilm regrowth after the sanitizing conditions are removed or halted. Chemical methods, where compatible, can be used on a wider variety of construction materials. These methods typically employ oxidizing agents such as halogenated compounds, hydrogen peroxide, ozone, peracetic acid, or combinations thereof. Halogenated compounds are effective sanitizers but are difficult to flush from the system and may leave biofilms intact. Compounds such as hydrogen peroxide, ozone, and peracetic acid oxidize bacteria and biofilms by forming reactive peroxides and free radicals (notably hydroxyl radicals). The short half-life of these compounds, particularly ozone, may require that it be added continuously during the sanitization process. Hydrogen peroxide and ozone rapidly degrade to water and oxygen; peracetic acid degrades to acetic acid in the presence of ultraviolet light. It is important to note that microorganisms in a biofilm can be extremely difficult to kill, even by aggressive oxidizing biocides. The less developed the biofilm, the more effective the biocidal action. Therefore, optimal biocide control is achieved by frequent biocide use that does not allow significant biofilm development between treatments.

In-line ultraviolet light at a wavelength of 254 nm can also be used to "sanitize" water in the system continuously, but these devices must be properly sized for the water flow. Such devices inactivate a high percentage of microorganisms that flow through the device but cannot be used to directly control existing biofilm upstream or downstream of the device. However, when coupled with conventional thermal or chemical sanitization technologies or located immediately upstream of a microbially retentive filter, it is most effective and can prolong the interval between system sanitizations. The use of ultraviolet light of the proper wavelength also facilitates the degradation of hydrogen peroxide and ozone, peracetic acid, and chlorinated water disinfectants.

Sanitization steps require validation to demonstrate the capability of reducing and holding microbial contamination at acceptable levels. Validation of thermal methods should include a heat distribution study to demonstrate that saniti-

zation temperatures are achieved throughout the system. Validation of chemical methods require demonstrating adequate chemical concentrations throughout the system. In addition, when the sanitization process is completed, effective removal of chemical residues must be demonstrated. The frequency of sanitization is generally dictated by the results of system monitoring. Conclusions derived from trend analysis of the microbiological data should be used as the alert mechanism for maintenance. The frequency of sanitization should be established in such a way that the system operates in a state of microbiological control and does not routinely exceed Alert Levels.

OPERATION, MAINTENANCE, AND CONTROL

A preventive maintenance program should be established to ensure that the water system remains in a state of control. The program should include (1) procedures for operating the system, (2) monitoring programs for critical quality attributes and operating conditions including calibration of critical instruments, (3) schedule for periodic sanitization, (4) preventive maintenance of components, and (5) control of changes to the mechanical system and to operating conditions.

Operating Procedures—Procedures for operating the water system and performing routine maintenance and corrective action should be written, and they should also define the point when action is required. The procedures should be well documented, detail the function of each job, assign who is responsible for performing the work, and describe how the job is to be conducted.

Monitoring Program—Critical quality attributes and operating parameters should be documented and monitored. The program may include a combination of in-line sensors or automated instruments (e.g., for TOC, conductivity, hardness, chlorine, etc.), automated or manual documentation of operational parameters (such as flow rates or pressure drop across a carbon bed, filter, or RO unit), and laboratory tests (e.g., total microbial counts). The frequency of sampling, the requirement for evaluating test results, and the necessity for initiating corrective action should be included.

Sanitization—Depending on system design and the selected units of operation, routine periodic sanitization may be necessary to maintain the system in a state of microbial control. Technologies for sanitization are described above.

Preventive Maintenance—A preventive maintenance program should be in effect. The program should establish what preventive maintenance is to be performed, the frequency of maintenance work, and how the work should be documented.

Change Control—The mechanical configuration and operating conditions must be controlled. Proposed changes should be evaluated for their impact on the whole system. The need to requalify the system after changes are made should be determined. Following a decision to modify a water system, the affected drawings, manuals, and procedures should be revised.

SAMPLING CONSIDERATIONS

Water systems should be monitored at a frequency that is sufficient to ensure that the system is in control and continues to produce water of acceptable quality. Samples should be taken from representative locations within the processing and distribution system. Established sampling frequencies should be based on system validation data and should cover critical areas including unit operation sites. The sampling plan should take into consideration the desired attributes of the water being sampled. For example, systems for *Water for Injection* because of their more critical microbiological requirements, may require a more rigorous sampling frequency.

Where possible, samples should be collected from use points using the same delivery devices, such as hoses, and procedures, such as preliminary hose or outlet flushing, as are employed for normal water use from those use points. Where use-points samples are not practical, special sampling ports may be used, but in both cases, consideration must be given to sample collection so that it accurately represents the quality attributes of the water delivered by the system. This may include sampling port or use-point sanitization and thorough flushing before a sample is taken if such practices are employed during routine water use or delivery from the system.

Samples containing chemical sanitizing agents require neutralization prior to microbiological analysis. Samples for microbiological analysis should be tested immediately or suitably protected to preserve the original microbial attributes until analysis can begin. Samples of flowing water are only indicative of the concentration of planktonic (free floating) microorganisms present in the system. Biofilm microorganisms (those attached to water system surfaces) are usually present in greater numbers and are the source of the planktonic population recovered from grab samples. Microorganisms in biofilms represent a continuous source of contamination and are difficult to directly sample and quantify. Consequently, the planktonic population is usually used as an indicator of system contamination levels and is the basis for system *Alert* and *Action Levels*. The consistent appearance of elevated planktonic levels is usually an indication of advanced biofilm development in need of remedial control. System control and sanitization are key in controlling biofilm formation and the consequent planktonic population.

CHEMICAL CONSIDERATIONS

The chemical attributes of *USP* waters prior to 1997 were specified by a series of chemistry tests for various specific and nonspecific attributes with the intent of detecting chemical species indicative of incomplete or inadequate purification. Many tests dated back to the 19th century, were nonquantitative, and represented long since outmoded analytical technologies. While these methods could have been considered barely adequate to control the quality of these waters, they nevertheless stood the test of time. This was partly because the operation of water systems was, and still is, based on on-line conductivity measurements and specifications generally thought to correlate with, or at least preclude, the failure of these archaic chemistry attribute tests.

In 1997, USP initiated a movement away from these chemical attribute tests to contemporary analytical technologies for the bulk waters *Purified Water* and *Water for Injection* The intent was to upgrade the analytical technologies without necessarily tightening the quality requirements. The two contemporary analytical technologies employed were total organic carbon (TOC) and conductivity. The TOC test replaced the test for *Oxidizable Substances* that primarily targeted organic contaminants. A multistaged *Conductivity* test which detects ionic (mostly inorganic) contaminants replaced, with the exception of the test for *Heavy Metals,* all of the inorganic chemical tests (i.e., *Ammonia, Calcium, Carbon Dioxide, Chloride, Sulfate*).

Replacing the heavy metals attribute was considered unnecessary because (a) the source water specifications (found in the NPDWR) for individual heavy metals were tighter than the empirically determined limit found in the *USP XXII Water for Injection* and *Purified Water* monograph tests (approximately 0.1 ppm), (b) contemporary water system construction materials do not leach heavy metal contaminants, and (c) test results for this attribute have uniformly been

negative—there has not been a confirmed occurrence of a singular test failure (failure of only the *Heavy Metals* test with all other attributes passing) since the current heavy metal drinking water standards have been in place. Nevertheless, since the presence of heavy metals in *Purified Water* or *Water for Injection*, however unlikely, could have dire consequences, its absence should at least be documented during new water system commissioning, validation, or through pre-1997 test results records.

The only remaining original ''inorganic'' tests not covered by the conductivity specifications were *Total Solids* and *pH. Total Solids* was considered largely redundant with the nonselective tests of conductivity and TOC for most chemical species other than silica, which could remain undetected in its colloidal form. Fortunately, colloidal silica in *Purified Water* and *Water for Injection* is easily removed by most water pretreatment steps and even if present in the water, constitutes no medical or functional hazard except under extreme and rare situations. In such extreme situations, other attribute extremes are also likely to be detected. Nevertheless, it is the user's responsibility to ensure fitness for use, so if silica is a significant component in the source water and the purification unit operations could be operated or fail in such a way as to selectively allow silica to be released into the finished water (in the absence of co-contaminants detectable by a significant conductivity response), then either silica-specific or a total solids type testing should be utilized by those few affected users to monitor and control this rather rare problem.

The *pH* attribute was eventually recognized to be redundant to the conductivity test (which included *pH* as an aspect of the test and specification), so *pH* was dropped as a separate attribute test.

The rationale used by USP to establish its conductivity specification took into consideration the conductivity contributed by the two least conductive former attributes of *Chloride* and *Ammonia,* thereby precluding their failure had those wet chemistry tests been performed. In essence, the Stage 3 conductivity specifications (see *Water Conductivity* ⟨645⟩) were established from the sum of the conductivities of contributing ions as a function of pH of chloride (from pH 5.0 to 6.2) or ammonia (from pH 6.3 to 7.0), plus the unavoidable contribution from water ions (H^+ and OH^-), dissolved atmospheric CO_2 (as HCO_3^-), and an electro-balancing quantity of either Na^+ of Cl^-, depending on the pH-induced ionic imbalance (see *Table 1*). The Stage 2 conductivity specification is the lowest value on this table, 2.1 µS/cm. The Stage 1 specifications, designed primarily for on-line measurements, were derived from summing the lowest values in each column for a series of tables similar to *Table 1*, but created for each 5° increment between 0° and 100°. For example purposes, the italicized values in *Table 1*, the conductivity data table for 25°, were summed to yield a conservative value of 1.3 µS/cm, the Stage 1 specification for a nontemperature compensated, nonatmosphere equilibrated water sample that actual had a measured temperature of 25° to 29°. Each 5° increment table was similarly treated to yield the individual values listed in the table of Stage 1 specifications (see *Water Conductivity* ⟨645⟩).

Table 1. Contributing Ion Conductivities of the Chloride–Ammonia Model as a Function of pH (in atmosphere-equilibrated water at 25°)

	Conductivity (μS/cm)						Combined	Stage 3
pH	H^+	OH^-	HCO_3^-	Cl^-	Na^+	NH_4^+	Conductivities	Limit
5.0	3.49	0	0.02	1.01	0.19	0	4.71	4.7
5.1	2.77	0	0.02	1.01	0.29	0	4.09	4.1
5.2	2.20	0	0.03	1.01	0.38	0	3.62	3.6
5.3	1.75	0	0.04	1.01	0.46	0	3.26	3.3
5.4	1.39	0	0.05	1.01	0.52	0	2.97	3.0
5.5	1.10	0	0.06	1.01	0.58	0	2.75	2.8
5.6	0.88	0	0.08	1.01	0.63	0	2.60	2.6
5.7	0.70	0	0.10	1.01	0.68	0	2.49	2.5
5.8	0.55	0	0.12	1.01	0.73	0	2.41	2.4
5.9	0.44	0	0.16	1.01	0.78	0	2.39	2.4
6.0	0.35	0	0.20	1.01	0.84	0	2.40	2.4
6.1	0.28	0	0.25	1.01	0.90	0	2.44	2.4
6.2	0.22	0	0.31	1.01	0.99	0	2.53	2.5
6.3	0.18	0	0.39	0.63	0	1.22	2.42	2.4
6.4	0.14	0.01	0.49	0.45	0	1.22	2.31	2.3
6.5	0.11	0.01	0.62	0.22	0	1.22	2.18	2.2
6.6	0.09	0.01	0.78	0	0.04	1.22	2.14	2.1
6.7	0.07	0.01	0.99	0	0.27	1.22	2.56	2.6
6.8	0.06	0.01	1.24	0	0.56	1.22	3.09	3.1
6.9	0.04	0.02	1.56	0	0.93	1.22	3.77	3.8
7.0	0.03	0.02	1.97	0	1.39	1.22	4.63	4.6

As mentioned above, this rather radical change to a conductivity attribute as well as the inclusion of a TOC attribute allowed on-line measurements, if desired. This was a major philosophical change for USP and allowed major savings to be realized by laboratories. The TOC and conductivity tests can also be performed "off-line" in the laboratories using collected samples, though sample collection tends to introduce opportunities for adventitious contamination that can cause false high readings. The collection of on-line data is not, however, without challenges. The essentially continuous readings tend to create voluminous amounts of data where before only a single data point was available. Contin-

uous data is excellent for understanding how a water system performs during all of its various usage and maintenance events in real time, but it tends to overwhelm quality control data systems that are designed for far less data. In such situations, the user must decide how to limit the data to be used for routine quality control purposes. Examples of acceptable approaches include using highest values for a given period, highest time-weighted average for a given period (from fixed or rolling subperiods), or values at a fixed daily time. Each approach has advantages and disadvantages relative to calculation complexity and reflection of continuous quality, so the user must decide which approach is most suitable or justifiable.

Packaged waters have presented a particular dilemma relative to the attributes of conductivity and TOC. The package itself is the source of chemicals (inorganics and organics) that leach over time into the water and can be easily detected. The irony of organic leaching from plastic packaging is that prior to the 1997 attribute changes for bulk monographed waters, when the *Oxidizable Substances* test was the only "organic contaminant" for both bulk and packaged waters, that test's insensitivity to those organic leachables rendered their presence in packaged water at high concentrations (many times the TOC specification for bulk water) virtually undetectable. Similarly, glass containers can also leach inorganics, such as sodium, which are easily detected by conductivity, but are virtually undetected by the specific wet chemistry tests, other than *pH* or *Total Solids,* included in the water monographs of that day. Fortunately, time has proven most of these leachables to be harmless at the rather significant concentrations present. Nevertheless, they effectively degrade the quality of the high-purity waters placed into these packaging system. Some packaging materials contain more leachables than others and may not be as suitable for holding water and maintaining its purity. In essence, the attributes of conductivity and TOC tend to reveal more about the packaging leachables than they do about the water's original purity. These "allowed" leachables may render the packaged versions of originally equivalent bulk water essentially unsuitable for many uses where the bulk waters are perfectly adequate.

MICROBIAL CONSIDERATIONS

The major exogenous source of microbial contamination of bulk pharmaceutical water is source or feed water. Feed water quality must, at a minimum, meet the quality attributes of *Drinking Water* for which the level of coliforms are regulated. A wide variety of other microorganisms, chiefly Gram-negative bacteria, may be present. These microorganisms may compromise subsequent purification steps. Examples of other potential exogenous sources of microbial contamination include unprotected vents, faulty air filters, backflow from contaminated outlets, drain airbreaks, and replacement activated carbon, deionizer resins, and regenerant chemicals. Sufficient care should be given to system design and maintenance in order to minimize microbial contamination from these exogenous sources.

Unit operations can be a major source of endogenous microbial contamination. Microorganisms present in feed water may adsorb to carbon beds, deionizer resins, filter membranes, and other unit operation surfaces and initiate the formation of a biofilm. In a high-purity water system, biofilm is an adaptive response by certain microorganisms to survive in this low nutrient environment. Downstream colonization can occur when microorganisms are sloughed off existing biofilm colonized surfaces and carried to other areas of the water system. Microorganisms may also attach to suspended particles such as carbon bed fines or fractured resin particles. When they become planktonic, they serve as

a source of contamination to subsequent purification equipment (compromising its functionality) and to distribution systems.

Another source of endogenous microbial contamination is the distribution system itself. Microorganisms can colonize pipe surfaces, valves, and other areas where they proliferate, forming a biofilm and becoming a continuous source of microbial contamination.

Endotoxins are lipopolysaccharides from the cell envelope that is external to the cell wall of Gram-negative bacteria. Gram-negative bacteria that form biofilms can become a source of endotoxins in pharmaceutical waters. Endotoxins may either be associated with living microorganisms or fragments of dead microorganisms, or they may be free molecules. The free form of endotoxins may be released from cell surfaces or biofilms that colonize the water system, or they may enter the water system via the feed water.

Endotoxin levels may be minimized by controlling the introduction of free endotoxins and microorganisms in the feed water and minimizing microbial proliferation in the system. This may be accomplished through the normal exclusion or removal action afforded by various unit operations within the treatment system as well as through system sanitization. Other control methods include the use of ultrafilters or charge-modified filters, either in-line or at the point of use. The presence of endotoxins may be monitored as described in the general test chapter *Bacterial Endotoxins Test* ⟨85⟩.

ENUMERATION CONSIDERATIONS

The objective of a water system microbiological monitoring program is to provide sufficient information to control and assess the microbiological quality of the water produced. Product quality requirements should dictate water quality needs. An appropriate level of control may be maintained by using data trending techniques and, if necessary, limiting specific contraindicated microorganisms. Consequently, it may not be necessary to detect all of the microorganisms present in a given sample. The monitoring program and methodology should indicate adverse trends and detect microorganisms that are potentially harmful to the finished product, process, or consumer. Final selection of method variables should be based on the individual requirements of the system being monitored.

It should be recognized that there is no single method that is capable of detecting all of the potential microbial contaminants of a water system. The methods used for microbial monitoring should be capable of isolating the numbers and types of organisms that have been deemed significant relative to system control and product impact for each individual system. Several criteria should be considered when selecting a method to monitor the microbial content of a pharmaceutical water system. These include method sensitivity, range of organisms recovered, sample throughput, incubation period, cost, and technical complexity. An alternative consideration to the use of the classical "culture" approaches is a sophisticated instrumental or hybrid approach that may yield more timely results. However, care must be exercised in selecting such an alternative approach to ensure that it has both sensitivity and correlation to classical culture approaches, which are generally considered to be the "gold standard" of microbial enumeration.

The Classical Culture Approach

Classical culture approaches for microbial testing of water include but are not limited to pour plates, spread plates, membrane filtration, and most probable number (MPN) tests. These methods are generally easy to perform, are less expensive, and provide excellent sample processing throughput. Method sensitivity can be increased via the use of larger sample sizes. This strategy is used in the mem-

brane filtration method. Culture approaches are further defined by the type of medium used in combination with the incubation temperature and duration. This combination should be selected according to the monitoring needs presented by a specific water system as well as its ability to recover microorganisms that could have a detrimental effect on the product or process.

There are two basic forms of media available for traditional microbiological analysis: ''high'' nutrient and ''low'' nutrient. High-nutrient media are intended as general media for the isolation and enumeration of heterotrophic or ''copiotrophic'' bacteria. Low-nutrient media may be beneficial for isolating slow growing ''oligotrophic'' bacteria and bacteria that require lower levels of nutrients to grow optimally. Low-nutrient and high-nutrient cultural approaches may be concurrently used, especially during the validation of a water system, as well as periodically thereafter, in order to determine if any additional numbers or types of bacteria are present so that their impact on the end use may be assessed. Additionally, the efficacy of system controls and sanitization on these slower growing bacteria can also be assessed.

Duration and temperature of incubation are also critical aspects of a microbiological test method. Classical methodologies using high nutrient media are typically incubated at 30° to 35° for 48 to 72 hours. Because of the flora in certain water systems, incubation at lower temperatures (e.g., 20° to 25°) for longer periods (e.g., 5 to 7 days) can recover higher microbial counts when compared to classical methods. Low-nutrient media are designed for these lower temperature and longer incubation conditions (sometimes as long as 14 days to maximize recovery of very slow growing oligotrophs or sanitant injured microorganisms), but even high-nutrient media can sometimes increase their recovery with these longer and cooler incubation conditions. Whether or not a particular system needs to be monitored using high- or low-nutrient media with higher or lower incubation temperatures or shorter or longer incubation times should be determined during or prior to system validation and periodically reassessed as the microbial flora of a new water system gradually establish a steady state relative to its routine maintenance and sanitization procedures. The establishment of a ''steady state'' can take months or even years and can be perturbed by a change in use patterns, a change in routine and preventative maintenance or sanitization procedures, and frequencies or any type of system intrusion, such as for component replacement, removal, or addition. The decision to use longer incubation periods should be made after considering the need for timely information and the type of corrective actions required when an *Alert* or *Action Level* is exceeded.

The advantages gained by incubating for longer times, namely recovery of injured microorganisms, slow growers, or more fastidious microorganisms, should be balanced against the need to have a timely investigation and to take corrective action, as well as the ability of these microorganisms to detrimentally affect products or processes. In no case, however, should incubation at 30° to 35° be less than 48 hours or less than 96 hours at 20° to 25°.

"Instrumental" Approaches

Examples of instrumental approaches include microscopic visual counting techniques (e.g., epifluorescence and immunofluorescence) and similar automated laser scanning approaches and radiometric, impedometric, and biochemically based methodologies. These methods all possess a variety of advantages and disadvantages. One advantage is their precision and accuracy. In general, instrument approaches often have a shorter lead time for obtaining results, which facilitates timely system control. This advantage, however, is often counterbalanced by limited sample processing throughput due to extended sample collection time, costly and labor-intensive sample processing, or other instrument and sensitivity limitations.

Instrumental approaches are typically destructive because further isolate manipulation for characterization purposes is precluded. Generally, some form of microbial isolate characterization may be a required element of water system monitoring. Consequently, culturing approaches have traditionally been preferred over instrumental approaches because they offer a balance of desirable test attributes and post-test capabilities.

Suggested Methodologies

The following general methods were originally derived from *Standard Methods for the Examination of Water and Wastewater,* 17th Edition, American Public Health Association, Washington, DC 20005. Even though this publication has undergone several revisions since its first citation in this *USP* chapter, the methods are still considered appropriate for establishing trends in the number of colony-forming units observed in the routine microbiological monitoring of pharmaceutical waters. It is recognized, however, that other combinations of media and incubation time and temperature may occasionally or even consistently result in higher numbers of colony-forming units being observed.

The extended incubation periods that are usually required by some of the alternative methods available offer disadvantages that may outweigh the advantages of the higher counts that may be obtained. The somewhat higher baseline counts that might be observed using alternate cultural conditions would not necessarily have greater utility in detecting an excursion or a trend. In addition, some alternate cultural conditions using low-nutrient media tend to lead to the development of microbial colonies that are much less differentiated in colonial appearance, an attribute that microbiologists rely on when selecting representative microbial types for further characterization. It is also ironical that the nature of some of the slow growers and the extended incubation times needed for their development into visible colonies may also lead to those colonies being largely nonviable, which limits their further characterization and precludes their subculture and identification.

Methodologies that can be suggested as generally satisfactory for monitoring pharmaceutical water systems are as follows. However, it must be noted that these are not referee methods nor are they necessarily optimal for recovering microorganisms from all water systems. The users must decide which methodologies are best for monitoring their water systems and recovering certain contraindicated species they may have specified.

Drinking Water:	POUR PLATE METHOD OR MEMBRANE FILTRATION METHOD[1]
	Sample Volume—1.0 mL minimum[2]
	Growth Medium—Plate Count Agar[3]
	Incubation Time—48 to 72 hours minimum
	Incubation Temperature—30° to 35°
Purified Water:	POUR PLATE OR MEMBRANE FILTRATION METHOD[1]
	Sample Volume—1.0 mL minimum[2]
	Growth Medium—Plate Count Agar[3]
	Incubation Time—48 to 72 hours minimum
	Incubation Temperature—30° to 35°
Water for Injection:	MEMBRANE FILTRATION METHOD[1]
	Sample Volume—100 mL minimum[2]
	Growth Medium—Plate Count Agar[3]
	Incubation Time—48 to 72 hours minimum
	Incubation Temperature—30°C to 35°C

[1] A membrane filter with an absolute rating of 0.45 µm is generally considered preferable even though the cellular width of some of the bacteria in the sample may be narrower than this. The efficiency of the filtration process still allows the retention of a very high percentage of these smaller cells and is adequate for this application. Filters with smaller porosity ratings may be used if desired, but for a variety of reasons the ability of the retained cells to develop into visible colonies may be compromised, so count accuracy must be verified by a reference approach.

[2] When colony counts are low to undetectable using the indicated minimum sample volume, it is generally recognized that a larger sample volume should be tested in order to gain better assurance that the resulting colony count is more statistically representative. The sample volume to consider testing is dependent on the user's need to know (which is related to the established *Alert* and *Action Levels* and the water system's microbial control capabilities) and the statistical reliability of the resulting colony count. In order to test a larger sample volume, it may be necessary to change testing techniques, e.g., changing from a Pour Plate to a Membrane Filtration approach. Nevertheless, in a very low to nil count scenario, a maximum sample volume of around 250 to 300 mL is usually considered a reasonable balance of sample collecting and processing ease and increased statistical reliability. However, when sample volumes larger than about 2 mL are needed, they can only be processed using the Membrane Filtration method.

[3] Also known as Standard Methods Agar, Standard Methods Plate Count Agar, or TGYA, this medium contains Tryptone (pancreatic digest of casein), Glucose and Yeast Extract.

IDENTIFICATION OF MICROORGANISMS

Identifying the isolates recovered from water monitoring methods may be important in instances where specific waterborne microorganisms may be detrimental to the products or processes in which the water is used. Microorganism information such as this may also be useful when identifying the source of microbial contamination in a product or process. Often a limited group of microorganisms are routinely recovered from a water system. After repeated recovery and characterization, an experienced microbiologist may become proficient at their identification based on only a few traits such as colonial morphology and staining characteristics. This level of characterization may be adequate for most situations.

ALERT AND ACTION LEVELS

Water systems should be microbiologically monitored to confirm that they continue to operate within their design specifications and produce water of acceptable quality. Monitoring data may be compared to established process parameters or product specifications.

A refinement to the use of process parameters and product specifications is the establishment of *Alert* and *Action Levels,* which signal a shift in process performance. *Alert* and *Action Levels* are distinct from process parameters and product specifications in that they are used for monitoring and control rather than accept or reject decisions. *Alert Levels* are levels, events, or ranges that, when exceeded, indicate that a process may have drifted from its normal operating condition. *Alert Levels* constitute a warning and do not necessarily require a corrective action. *Action Levels* are levels, events, or ranges that, when exceeded, indicate that a process has drifted from its normal operating range. Exceeding an *Action Level* indicates that corrective action should be taken to bring the process back into its normal operating range. *Alert* and *Action Levels* are established within process and product specification tolerances and are based on a combination of technical and product related considerations. Consequently, exceeding an *Alert* or *Action Level* does not imply that product quality has been compromised.

Technical considerations used to establish *Alert* and *Action Levels* should include a review of equipment design specifications to ensure that the purification equipment is capable of achieving the required level of purity. In addition, samples should be collected and analyzed over a period of time to develop data reflecting normal water quality trends. Historical or statistically based levels can be established using the above data. Levels established in this way measure process performance and are independent of product concerns.

Product-related *Alert* and *Action Levels* should represent both product quality concerns and the ability to effectively manage the purification process. These levels are typically based on a review of process data and an assessment of pro-

duct sensitivity to chemical and microbiological contamination. The assessment of product susceptibility might include preservative efficacy, water activity, pH, etc. The levels should be set such that, when exceeded, product quality is not compromised. Monitoring data should be analyzed on an ongoing basis to ensure that the process continues to perform within acceptable limits. An analysis of data trends is often used to evaluate process performance. This information can be used to predict departures from established operating parameters, thereby signaling the need for appropriate preventative maintenance.

It should be recognized that the microbial *Alert* and *Action Levels* established for any pharmaceutical water system are necessarily linked to the monitoring method chosen. Using the suggested methodologies above, generally considered maximum *Action Levels* are 500 colony-forming units (cfu) per mL for *Drinking Water,* 100 cfu per mL for *Purified Water* and 10 cfu per 100 mL for *Water for Injection.* However, if a given water system controls microorganisms much more tightly than these levels, appropriate *Alert* and *Action Levels* should be lower to truly indicate when water systems may be starting to trend out of control. It is appropriate that, where possible, these in-process control parameters should be established well below microbial levels that could be problematic for products and processes where used.

It should be emphasized that these in-process control guidelines are not intended to be totally inclusive for every situation where ingredient waters are employed. For example, Gram-negative microorganisms are not excluded from ingredient waters, nor is the presence of Gram-negative microorganisms prohibited in *Drinking Water* in the Federal Regulations. The reason for this is that these microorganisms are ubiquitous to the aqueous environment and their exclusion would likely require a sterilization process that would not be appropriate or feasible in many manufacturing scenarios. However, there are situations where they might not be tolerated in certain products, such as some topical products intended for use on broken skin or in some oral dosage forms. It is, therefore, incumbent upon the manufacturer to supplement the general in-process control guidelines to fit each particular manufacturing and product use situation.■2S (*USP27*)

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

***N,N*-Dimethylformamide Diethyl Acetal.** This new reagent is used in *Standard solution 2* of *Test 1* in the *Related compounds* test under *Flumazenil*, which appears elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—39640-3

Add the following:

■***N,N*-Dimethylformamide Diethyl Acetal—147.22** [*1188-33-6*]—Use a suitable grade.[10] ■2S (*USP27*)

BRIEFING

Methyl Yellow. It is proposed to add this new reagent, which is used to prepare the *Methyl Yellow TS* employed in the *Assay* test in the monograph for *Cetylpyridinium Chloride Lozenges*.

(HDQ: M. Marques) RTS—40011-1

Add the following:

■**Methyl Yellow** *(p-Dimethylaminoazobenzene),* $C_{14}H_{15}N_3$—**225.3** [*60-11-7*]—Use a suitable grade. ■2S (*USP27*)

BRIEFING

Sodium Hydrogen Sulfate (*Sodium Bisulfate*)**.** This new reagent is used as a component of the *Mobile phase* in the test for *Related compounds* in the proposed monograph for *Mefloquine Hydrochloride*, which appears elsewhere in this number of *PF*.

(HDQ: M. Marques) RTS—38976-1

Add the following:

■**Sodium Hydrogen Sulfate** (*Sodium Bisulfate*), $NaHSO_4$—**120.06** [*7681-38-1*]—Freely soluble in water; very soluble in boiling water. It decomposes in alcohol into sodium sulfate and free sulfuric acid. Use a suitable reagent grade.

Melting point ⟨741⟩: about 315°. ■2S (*USP27*)

BRIEFING

Tuberculin, Purified Protein Derivative. This new reagent is used as a component of the *Tuberculin solution* in the test for *Tuberculin sensitivity* in the proposed monograph *BCG Live*, which appears elsewhere in this number of *PF*.

(VVI: L. Bhattacharyya) RTS—40080-1

Add the following:

■**Tuberculin, Purified Protein Derivative** *(Tuberculin PPD)*—Derived from the human strain of *Mycobacterium tuberculosis*, and available either as a solution or as a lyophilized powder. For lyophilized powder, reconstitute according to the manufacturer's instructions using the diluent provided by the manufacturer. Solutions may contain a stabilizer and a preservative. One Tuberculin Unit (TU) is equivalent to 0.02 µg of Tuberculin PPD. ■2S (*USP27*)

Test Solutions

BRIEFING

Methyl Yellow TS, *USP 26* page 2529 and page 3012 of the *First Supplement*. It is proposed to update the preparation of this solution employed in the *Assay* test in the monograph for *Cetylpyridinium Chloride Lozenges*.

(HDQ: M. Marques) RTS—40011-1

Change to read:

Methyl Yellow TS~~— Dilute with alcohol a commercially available stock solution of methyl yellow in alcohol[S6] to obtain a solution having a concentration of 0.10 mg per mL.~~

■Prepare a solution containing 0.10 mg per mL in alcohol. ■2S (*USP27*)

In-Process Revision

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 26* page 2540, page 3179 of the *Second Supplement*, and page 1262 of *PF* 29(4) [Mar.–Apr. 2003].

(HDQ) RTS—39903-2; 39903-3

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are, or will be, official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Change to read:	
Acepromazine Maleate Tablets	~~W~~ ■T, ■1S (*USP27*) LR
Change to read:	
Acetaminophen, Aspirin, and Caffeine Tablets	~~W~~ ■T ■1S (*USP27*)
Change to read:	
Acetazolamide Tablets	~~W~~ ■T ■1S (*USP27*)
Change to read:	
Acetohexamide Tablets	~~W~~ ■T ■1S (*USP27*)
Change to read:	
Albuterol Tablets	~~W~~ ■T, ■1S (*USP27*) LR
Add the following:	
■Alendronate Sodium Tablets	T ■1S (*USP27*)
Change to read:	
Allopurinol Tablets	~~W~~ ■T ■1S (*USP27*)
Change to read:	
Alumina and Magnesia Tablets	~~W~~ ■T ■1S (*USP27*)
Change to read:	
Alumina, Magnesia, and Calcium Carbonate Tablets	~~W~~ ■T ■1S (*USP27*)
Change to read:	
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets	~~W~~ ■T ■1S (*USP27*)
Add the following:	
■Benazepril Tablets	W ■1S (*USP27*)
Add the following:	
■Bisoprolol Fumarate and Hydrochlorothiazide Tablets	W ■1S (*USP27*)
Add the following:	
■Black Cohosh Tablets	T, LR ■1S (*USP27*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W ■1S (*USP27*)
Add the following:	
■Fluoxetine Capsules, Delayed-Release	T ■1S (*USP27*)
Add the following:	
■Gabapentin Capsules	W ■1S (*USP27*)
Add the following:	
■Ginkgo Capsules	T, LR ■1S (*USP27*)
Add the following:	
■Ginkgo Tablets	T, LR ■1S (*USP27*)

Monograph Title	*Container Specification*
Add the following:	
■Irbesartan Tablets	W■1S (*USP27*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W■1S (*USP27*)
Add the following:	
■Isosorbide Mononitrate Tablets	T■2S (*USP27*)
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■2S (*USP27*)
Add the following:	
■Isradipine Capsules	T■1S (*USP27*)
Add the following:	
■Kava Capsules	T, LR■1S (*USP27*)
Add the following:	
■Kava Tablets	T, LR■1S (*USP27*)
Add the following:	
■Loratadine Tablets	T■1S (*USP27*)
Add the following:	
■Misoprostol Tablets	T■1S (*USP27*)
Add the following:	
■Naratriptan Tablets	T■1S (*USP27*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■1S (*USP27*)
Add the following:	
Oxaprozin Tablets	T, LR
Add the following:	
■Paroxetine Hydrochloride Tablets	W■1S (*USP27*)
Add the following:	
■Quinapril Tablets	W■1S (*USP27*)
Add the following:	
■Valsartan Capsules	T, LR■1S (*USP27*)
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■1S (*USP27*)

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 26* page 2546, page 3179 of the *Second Supplement*, page 5310 of *PF* 23(6) [Nov.–Dec. 1997], page 7017 of *PF* 24(5) [Sept.–Oct. 1998], page 8282 of *PF* 25(3) [May–June 1999], page 8589 of *PF* 25(4) [July–Aug. 1999], page 8917 of *PF* 25(5) [Sept.–Oct. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 504 of *PF* 26(2) [Mar.–Apr. 2000], page 837 of *PF* 26(3) [May–June 2000], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1385 of *PF* 26(5) [Sept.–Oct. 2000], page 1907 of *PF* 27(1) [Jan.–Feb. 2001], page 2281 of *PF* 27(2) [Mar.–Apr. 2001], page 2839 of *PF* 27(4) [July–Aug. 2001], page 3374 of *PF* 27(6) [Nov.–Dec. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 853 of *PF* 28(3) [May–June 2002], page 1236 of *PF* 28(4) [July–Aug. 2002], page 1542 of *PF* 28(5) [Sept.–Oct. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 509 of *PF* 29(2) [Mar.–Apr. 2003], page 812 of *PF* 29(3) [May–June 2003], and page 1262 of *PF* 29(4) [July–Aug. 2003].

(HDQ) RTS—37377-1; 38976-1; 39640-5; 40038-1; 40048-1; 40196-1

Add the following:

■**Calcitriol:** White or almost white crystals. Freely soluble in alcohol; soluble in ether and in fatty oils; practically insoluble in water. It is sensitive to air, heat, and light.■2S (*USP27*)

Add the following:

■**Camphorated Phenol Topical Gel:** Clear, colorless, oily gel.■2S (*USP27*)

Add the following:

■**Clopidogrel Bisulfate:** White to off-white powder. Freely soluble in water and in methanol; practically insoluble in ether.■2S (*USP27*)

In-Process Revision

Add the following:

■**Flumazenil:** White to off-white powder. Slightly soluble in acidic aqueous solutions; practically insoluble in water.■2S (*USP27*)

Add the following:

■**Mefloquine Hydrochloride:** White or slightly yellow, crystalline powder. Freely soluble in methanol; soluble in alcohol; very slightly soluble in water.■2S (*USP27*)

Add the following:

■**Metronidazole Benzoate:** White to slightly yellow, crystalline powder. Freely soluble in methylene chloride; soluble in acetone; slightly soluble in alcohol; very slightly soluble in ethyl ether; practically insoluble in water.■2S (*USP27*)

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"—See PF Vol. 29 No. 4, page 983.
Significant Figures and Tolerances—See PF Vol. 29 No. 4, page 984.
Tests and Assays—See PF Vol. 29 No. 4, page 985.
Preservation, Packaging, Storage, and Labeling—See PF Vol. 29 No. 4, page 988.

USP MONOGRAPHS

Acebutolol Hydrochloride Capsules—See PF Vol. 27 No. 1, page 1743.
Acepromazine Maleate—See PF Vol. 27 No. 3, page 2493.
Acepromazine Maleate Injection—See PF Vol. 27 No. 3, page 2494.
Acepromazine Maleate Tablets—See PF Vol. 27 No. 3, page 2494.
Acetaminophen—See PF Vol. 27 No. 3, page 2494.
Acetaminophen Capsules—See PF Vol. 27 No. 3, page 2494.
Acetaminophen for Effervescent Oral Solution—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Oral Solution—See PF Vol. 27 No. 3, page 2494.
Acetaminophen Oral Suspension—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Suppositories—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Tablets—See PF Vol. 27 No. 3, page 2495.
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Hydrochloric Acid, Alcoholic, Tenth-Molar (0.1 M)—See PF Vol. 28 No. 4, page 1235.
0.01 N Iodine VS—See PF Vol. 29 No. 3, page 812.
Lead Nitrate, Hundredth-Molar (0.01 M)—See PF Vol. 29 No. 4, page 1256.
Potassium Hydroxide, Alcoholic, Tenth Molar (0.1 M)—See PF Vol. 28 No. 4, page 1235.
Tetrabutylammonium Hydroxide in Methanol/Isopropyl Alcohol, 0.1 N—See PF Vol. 29 No. 2, page 508.

Reagent Footnotes,

Reagent Footnotes—See PF Vol. 29 No. 4, pages 1257–1262.
Footnote 85—See PF Vol. 26 No. 4, page 1133.
Footnote 87—See PF Vol. 26 No. 5, page 1383.
Footnote 99—See PF Vol. 27 No. 6, page 3374.
Footnote 100—See PF Vol. 27 No. 6, page 3374.
Footnote 101—See PF Vol. 27 No. 6, page 3374.
Footnote 102—See PF Vol. 27 No. 6, page 3374.
Footnote 103—See PF Vol. 28 No. 2, page 554.
Footnote 105—See PF Vol. 28 No. 6, page 1952.
Footnote 106—See PF Vol. 29 No. 1, page 266.
Footnote 107—See PF Vol. 29 No. 2, page 508.
Footnote 109—See PF Vol. 29 No. 2, page 508.
Footnote 110—See PF Vol. 29 No. 4, page 1262.
Footnote 111—See PF Vol. 29 No. 4, page 1262.

REFERENCE TABLES

Container Specifications for Capsules and Tablets—See PF Vol. 25 No. 5, page 8860; PF Vol. 25 No. 6, page 9176; PF Vol. 26 No. 1, page 145; PF Vol. 26 No. 3, page 836; PF Vol. 26 No. 4, page 1133; PF Vol. 26 No. 5, page 1384; PF Vol. 27 No. 1, page 1906; PF Vol. 27, No. 3, page 2597; PF Vol. 27 No. 4, page 2838; PF Vol. 27 No. 5, page 3118; PF Vol. 28 No. 3, page 852; PF Vol. 28 No. 4, page 1235; PF Vol. 28 No. 6, page 1952; PF Vol. 29 No. 1, page 266; PF Vol. 29 No. 2, page 508; PF Vol. 29 No. 4, page 1262.
Description and Relative Solubility of USP and NF Articles—See PF Vol. 23 No. 6, page 5310; PF Vol. 24 No. 5, page 7017; PF Vol. 25 No. 3, page 8282; PF Vol. 25 No. 4, page 8589; PF Vol. 25 No. 5, page 8917; PF Vol. 25 No. 6, page 9254; PF Vol. 26 No. 2, page 504 and 505; PF Vol. 26 No. 3, page 837;

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PF Vol. 26 No. 4, page 1135; PF Vol. 26 No. 5, page 1385; PF Vol. 27 No. 1, page 1907; PF Vol. 27 No. 2, page 2281; PF Vol. 27 No. 4, page 2839; PF Vol. 27 No. 5, page 3120; PF Vol. 27 No. 6, page 3374; PF Vol. 28 No. 2, page 554; PF Vol. 28 No. 3, page 853; PF Vol. 28 No. 4, page 1236; PF Vol. 28 No. 5, page 1542; PF Vol. 28 No. 6, page 1953; PF Vol. 29 No. 1, page 266; PF Vol. 29 No. 2, page 509; PF Vol. 29 No. 3, page 812; PF Vol. 29 No. 4, page 1262.

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Powdered Chaste Tree—See PF Vol. 29 No. 4, page 1268.
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Chondroitin Sulfate Sodium—See PF Vol. 29 No. 4, page 1270.
Chondroitin Sulfate Tablets—See PF Vol. 29 No. 3, page 692.
Cod Liver Oil—See PF Vol. 29 No. 4, page 1019.
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Docosahexaenoic Acid Capsules—See PF Vol. 26 No. 6, page 1651.
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Fish Oil Rich in Omega-3 Acids—See PF Vol. 29 No. 4, page 1272.
Fish Oil Rich in Omega-3 Acids Capsules—See PF Vol. 29 No. 4, page 1278.
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American Ginseng—See PF Vol. 27 No. 2, page 2243.
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Glucosamine and Chondroitin Sulfate Tablets—See PF Vol. 29 No. 3, page 698.
Goldenseal—See PF Vol. 27 No. 2, page 2255.
Powdered Hawthorn Leaf with Flower—See PF Vol. 26 No. 5, page 1362.
Kava—See PF Vol. 28 No. 1, page 100.
Powdered Kava—See PF Vol. 28 No. 1, page 104.
Powdered Kava Extract—See PF Vol. 28 No. 3, page 815.
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Lutein—See PF Vol. 29 No. 2, page 470.
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Oil- and Water-Soluble Vitamins Tablets—See PF Vol. 28 No. 5, page 1544.
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Saw Palmetto Extract—See PF Vol. 26 No. 6, page 1567.
Powdered St. John's Wort Extract—See PF Vol. 29 No. 3, page 702.
Valerian Capsules—See PF Vol. 27 No. 1, page 1825.
Water-Soluble Vitamins with Minerals Capsules—See PF Vol. 28 No. 5, page 1547.
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GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"—See PF Vol. 28 No. 1, page 88.

NF MONOGRAPHS

Alfadex—See PF Vol. 29 No. 4, page 1092.
Amminio Methacrylate Copolymer Dispersion—See PF Vol. 28 No. 2, page 628.
Ammonium Sulfate—See PF Vol. 29 No. 1, page 136.
Aspartame Acesulfame—See PF Vol. 29 No. 2, page 453.
Butylparaben—See PF Vol. 28 No. 2, page 572.
Candelilla Wax—See PF Vol. 29 No. 1, page 138.
Caprylocaproyl Macrogolglycerides—See PF Vol. 29 No. 3, page 688.
Carbomer Copolymer—See PF Vol. 29 No. 3, page 691.
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Carboxymethylcellulose Calcium—See PF Vol. 23 No. 6, page 5063.
Low-Substituted Carboxymethylcellulose Sodium—See PF Vol. 29 No. 4, page 1095.
Carboxymethylcellulose Sodium Suspension—See PF Vol. 25 No. 3, page 8088.
Cellulose Acetate Butyrate—See PF Vol. 25 No. 2, page 7861.
Cetrimonium Bromide—See PF Vol. 29 No. 1, page 139.
Copovidone—See PF Vol. 29 No. 4, page 1097.
Corn Syrup—See PF Vol. 28 No. 2, page 403.
Corn Syrup Solids—See PF Vol. 28 No. 6, page 1894.
High Fructose Corn Syrup—See PF Vol. 28 No. 2, page 408.
Cottonseed Oil, Hydrogenated—See PF Vol. 29 No. 1, page 141.
Croscarmellose Sodium—See PF Vol. 23 No. 3, page 4007.
Crospovidone—See PF Vol. 24 No. 1, page 5482.
Dibutyl Phthalate—See PF Vol. 29 No. 3, page 693
Diethylene Glycol Monostearate—See PF Vol. 29 No. 3, page 695.
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Ethylene Glycol Monostearate—See PF Vol. 29 No. 3, page 696.
Ethylparaben—See PF Vol. 28 No. 2, page 574.
Gellan Gum—See PF Vol. 29 No. 2, page 462.
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Glyceryl Monooleate—See PF Vol. 29 No. 2, page 468.
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Lauroyl Macrogolglycerides—See PF Vol. 26 No. 2, page 456.
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Magnesium Stearate—See PF Vol. 29 No. 2, page 474.
Maltitol Solution—See PF Vol. 29 No. 4, page 1111.
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Methylparaben—See PF Vol. 28 No. 52 page 575.
Oleic Acid—See PF Vol. 29 No. 3, page 701.
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Oral Solution Vehicle—See PF Vol. 29 No. 4, page 1114.
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Peanut Oil—See PF Vol. 29 No. 4, page 1117.
Phenolsulfonphthalein—See PF Vol. 28 No. 6, page 1899.
2-Phenoxyethanol—See PF Vol. 28 No. 6, page 1900.
Polyethylene Glycol—See PF Vol. 29 No. 3, page 702.

Polyethylene Glycol Ointment—See PF Vol. 29 No. 3, page 702.
Polyisobutylene—See PF Vol. 29 No. 1, page 150.
Polyoxyl Lauryl Ether—See PF Vol. 29 No. 4, page 1117.
Polyoxyl Stearyl Ether—See PF Vol. 29 No. 4, page 1118.
Polyoxyl Oleate—See PF Vol. 29 No. 4, page 1121.
Propylene Glycol Monostearate—See PF Vol. 29 No. 2, page 479.
Propylparaben—See PF Vol. 28 No. 2, page 581.
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Sorbitol Solution—See PF Vol. 28 No. 3, page 787.
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Hydrogenated Soybean Oil—See PF Vol. 29 No. 3, page 704.
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Purified Stearic Acid—See PF Vol. 29 No. 3, page 706.
Stearoyl Macrogolglycerides—See PF Vol. 29 No. 4, page 1135.
Sunflower Oil—See PF Vol. 27 No. 4, page 2803.
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Tobramycin Inhalation Solution—See PF Vol. 28 No. 3, page 789.
Tolu Balsam Syrup—See PF Vol. 28 No. 5, page 1467.
Tolu Balsam Tincture—See PF Vol. 28 No. 5, page 1468.
Tribasic Sodium Phosphate—See PF Vol. 29 No. 1, page 162.
Medium-Chain Triglycerides—See PF Vol. 29 No. 2, page 475.

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled

(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)

[*PF* 29(1)–*PF* 29(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals*		
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General Notices			
Preservation, Packaging, Storage, and Labeling	26	3	653
USP Monographs			
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water*	28	5	1390
Bacitracin—*Identification*	28	3	745
Cabergoline (new)	24	6	7141
Cabergoline Tablets (new)	24	6	7142
Carbon Dioxide—*Air*, *Assay*	28	4	1082
Carboxymethylcellulose Sodium—*Harmonization* (entire submission)	26	5	1403
Cefuroxime Axetil Tablets—*Dissolution Test 2*	27	2	2128
Desonide (new)	22	3	2275
Desonide Cream (new)	22	3	2276
Desonide Ointment (new)	22	3	2277
Dihydroergotamine Mesylate (entire submission)	24	1	5562
Dihydroergotamine Mesylate Injection—*Chromatographic purity*, *Assay*	24	1	5564
Enalaprilat Injection (new)	19	4	5587
Enoxaparin Sodium (new)	22	6	3031
Enoxaparin Sodium Injection (new)	22	6	3038
Epinephryl Borate Ophthalmic Solution—*USP Reference standards*, *Assay*	23	3	3991
Fluoxetine Capsules—*Chromatographic purity*, *Related compounds*, *Assay*	27	2	2150
Gabapentin (new)	27	5	3004
†Hydrocodone Bitartrate and Acetaminophen Tablets—*Labeling, Dissolution*	27	6	3301
Ketamine Hydrochloride—*Assay*	28	4	1140
†Levonorgestrel—*Limit of ethylsecothindrone*	27	3	2565
Mecamylamine Hydrochloride (entire submission)	28	2	320
Hydroxypropyl Methylcellulose—*Harmonization* (new)	24	5	6726
Methylcellulose—*Harmonization* (new)	24	5	6737
†Methylprednisolone Acetate for Rectal Suspension—*Packaging and storage*	27	1	1803
†Miconazole Nitrate Cream—*Assay*	26	5	1302
†Minocycline Hydrochloride—*Chromatographic purity, Assay*	28	3	770
Montelukast Sodium (new)	24	6	7160
Montelukast Sodium Tablets (new)	24	6	7162
Morphine Sulfate Extended-Release Capsules (new)	25	4	8426
†Nitrofurantoin Extended-Release Capsules (new)	25	5	8853
†Ondansetron Hydrochloride—*Limit of ondansetron related compound D*	29	1	92
Oxybutynin Chloride—*Chromatographic purity*	26	6	1561
Perflutren Protein-Type A Microspheres for Injection [Former title: Albumin Encapsulated Octafluoropropane Microspheres for Injection] (new)	27	4	2769
Povidone (entire submission)	22	6	3163
Sertraline Hydrochloride (new)	24	6	7179
Sertraline Hydrochloride Tablets (new)	24	6	7181
†Somatropin (new)	25	4	8540
†Somatropin for Injection (new)	25	4	8551
Sulindac—*Chromatographic purity*	25	5	8879
Sulindac Tablets	25	5	8880
Sunflower Oil—*Briefing*	27	4	2779
†Sutilains (new)	27	2	2199
†Sutilains Ointment (new)	27	2	2201
Titanium Dioxide (new)	24	2	5796
Vancomycin—*Chromatographic purity*, *Labeling*	27	4	2783
Vancomycin Hydrochloride—*Labeling*, *Other requirements*	27	4	2784
Vancomycin Injection—*Chromatographic purity*	27	4	2784

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled (*continued*)
(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)
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Vancomycin Hydrochloride for Injection—*Chromatographic purity*	27	4	2786
Vancomycin for Injection (entire submission)	27	4	2785
Sterile Vancomycin Hydrochloride—*Title*	27	4	2786
Sterile Water for Injection—*pH*, *Other requirements*	27	4	2787
Sterile Purified Water	28	4	1272
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
†*USP Gabapentin Related Compound C RS*	25	6	9222
†*USP Nabumetone Alcohol RS*	25	6	9222
†*USP Oxybutynin Chloride Related Compound A RS*	26	6	1606
†*USP Paroxetine Related Compound D RS*	25	3	8222
USP Povidone RS	20	5	8060
USP Sulindac Related Compound A RS	25	5	8893
†⟨41⟩ Weights and Balances (entire submission)	26	6	1607
†⟨61⟩ Microbial Limit Tests—*Harmonization*	27	2	2299
†⟨62⟩ Microbiological Procedures for Absence of Objectionable Microorganisms—*Harmonization*	27	2	2313
⟨71⟩ Sterility Tests (entire submission)	26	4	1102
†⟨581⟩ Vitamin D Assay—*Biological method*	26	4	1111
⟨661⟩ Containers—*Polypropylene Containers* (added)	26	4	1117
⟨786⟩ Particle Size Distribution Estimation by Analytical Sieving—*Harmonization*	25	1	7460
USP General Information Chapters			
⟨1010⟩ Analytical Data—Interpretation and Treatment	27	5	3086–3100
†⟨1151⟩ Pharmaceutical Dosage Forms—*Stability*	26	2	499
⟨1186⟩ Shipping and Storage of Labile Preparations	28	2	495
Dietary Supplements Monographs			
†Asian Ginseng Capsules (new)	26	3	775
†Saw Palmetto Capsules—*Disintegration and dissolution*	26	6	1571
NF Monographs			
Benzyl Alcohol (entire submissions)	27	4	2790, 2855
Cellulose Acetate	23	5	4677
Dimethicone—*Bacterial endotoxins*	28	3	813
Hydroxyethyl Cellulose (entire submission)	20	6	8311
Hydroxypropyl Beta Cyclodextrin (new)	24	6	7284
Silicon Dioxide (entire submission)	24	6	7191
Colloidal Silicon Dioxide—*Harmonization*	24	6	7187, 7194
Sodium Starch Glycolate (entire submission)	22	6	3202
Rice Starch (new)	23	4	4348
Stearic Acid—*Harmonization*	20	6	8313
	28	2	583
Sucrose (entire submission)	22	6	3206
Reagents, Indicators, and Solutions			
†0.5 M Copper Sulfate Solution (new)	26	5	1382
†Cyclohexylmethanol (new)	25	1	7582
†Dicyclohexyl (new)	25	1	7582
†17α-Estradiol (new)	27	2	2278
†Ethylbenzene (new)	25	1	7582
2-Isopropylphenol (new)	27	4	2838
Reagent Footnotes			
Footnote 108	29	2	508

†New cancellations in 29(5).

In-Process Revision

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

MONOGRAPHS (USP)

BRIEFING

Alcohol, *USP 26* page 59 and page 2507 of *PF* 27(3) [May–June 2001]. The European Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of compendial standards for the *Alcohol* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION Stage 6** document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia.

Differences between the **ADOPTION Stage 6** document and the current *USP* monograph include the following:

(1) Definition—No change.
(2) *Packaging and storage*—Storage conditions to protect from light are added.
(3) *USP Reference standards*—A reference standard for Alcohol is added for use in the *Identification* test.
(4) *Identification*—Tests *A* and *B* are replaced with a more definitive infrared absorption test, and the test for specific gravity is moved under *Identification*.
(5) *Clarity of solution*—This test is added to comply with EP standards.
(6) *Color of solution*—This test is added to comply with EP standards.
(7) *Specific gravity*—No change.
(8) *Acidity*—This test is replaced by a test for *Acidity or alkalinity* to comply with EP standards.
(9) *Limit of nonvolatile residue*—The sample size in increased from 40 to 100 mL.
(10) *Water-insoluble substances*—This test is deleted. Because the monograph contains tests for *Nonvolatile residue* and *Volatile impurities,* this test is no longer needed.
(11) *Aldehydes and other foreign organic substances*—This test is replaced with a *Volatile impurities* test.
(12) *Amyl alcohol and nonvolatile, carbonizable substances*—This test is replaced with a *Volatile impurities* test.
(13) *Ultraviolet absorbance*—This test is added to comply with EP standards.
(14) *Limit of acetone and isopropyl alcohol*—This test is replaced with a *Volatile impurities* test.
(15) *Methanol*—This test is replaced with a *Volatile impurities* test.
(16) *Volatile impurities*—This chromatographic test is added to limit a wide array of volatile impurities within a single test method.

(EMC: J. Lane) RTS—40109-1

Add the following:

Alcohol

C_2H_6O 46.07

Ethanol.

Ethyl alcohol [*64-17-5*].

» Alcohol contains not less than 92.3 percent and not more than 93.8 percent, by weight, corresponding to not less than 94.9 percent and not more than 96.0 percent, by volume, at 15.56°, of C_2H_5OH.

Packaging and storage—Preserve in tight containers, protected from light, and remote from heat, sparks, or open flames.

USP Reference standards ⟨11⟩**—***USP Alcohol RS.*

Clarity of solution—[NOTE—The *Test solution* is to be compared to *Reference suspension A* and to water in diffused daylight 5 minutes after preparation of *Reference suspension A.*]

Hydrazine solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of *Hydrazine solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension A.* Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension B.*

Test solution A—The substance to be examined.

Test solution B—Dilute 1.0 to 20 mL with water, and allow to stand for 5 minutes before testing.

Procedure—Transfer a sufficient portion of *Test solution A* and *Test solution B* to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A, Reference suspension B,* and water to separate matching test tubes. Compare *Test solution A, Test solution B, Reference suspension A, Reference suspension B,* and water in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The diffusion of light must be such that *Reference suspension A* can readily be distinguished from water, and that *Reference suspension B* can readily be distinguished from *Reference suspension A.*] *Test solution A* and *Test solution B* show the same clarity as that of water or their opalescence is not more pronounced than that of *Reference suspension A.*

Color of solution—

Standard stock solution—Combine 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, 2.4 mL of cupric sulfate CS, and 1.6 mL of dilute hydrochloric acid (10 g per L).

Standard solution—[NOTE—Prepare the *Standard solution* immediately before use.] Transfer 1.0 mL of *Standard stock solution* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix.

Test solution—The substance to be examined.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard solution* and water to separate, matching test tubes. Compare the *Test solution, Standard solution,* and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* has the appearance of water or is not more intensely colored than the *Standard solution.*

Identification—

A: It complies with the test for *Specific gravity.*

B: *Infrared Absorption* ⟨197F⟩ or ⟨197S⟩ neat.

Specific gravity ⟨841⟩**:** between 0.812 and 0.816 at 15.56°, indicating between 92.3% and 93.8%, by weight, or between 94.9% and 96.0%, by volume, of C_2H_5OH.

Acidity or alkalinity—

Phenolphthalein solution—Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol, and dilute with water to 100 mL.

Procedure—To 20 mL of alcohol, add 20 mL of freshly boiled and cooled water and 0.1 mL of *Phenolphthalein solution*. The solution is colorless. Add 1.0 mL of 0.01 N sodium hydroxide. The solution is pink (30 ppm, expressed as acetic acid).

Ultraviolet absorption—Record the UV absorption spectrum of the test material from 200 to 400 nm in a 1-cm cell: maximum absorbance 0.40 at 240 nm, 0.30 between 250 and 260 nm, and 0.10 between 270 and 340 nm. Examine between 235 and 340 nm, in a 5-cm cell, using water as the compensation liquid. The absorption curve is smooth.

Volatile impurities—

Test solution A—The substance to be examined.

Test solution B—Add 150 µL of 4-methylpentan-2-o1 to 500.0 mL of the substance to be examined.

Standard solution A—Dilute 100 µL of methanol to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Standard solution B—Dilute 50 µL of methanol and 50 µL of acetaldehyde to 50.0 mL with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

Standard solution C—Dilute 150 µL of acetal to 50.0 mL with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

Standard solution D—Dilute 100 µL of benzene to 100.0 mL with the substance to be examined. Dilute 100 µL of the solution to 50.0 mL with the substance to be examined.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, maintained at about 280°, and a 0.32-mm × 30-m fused silica capillary column bonded with a 1.8-µm layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm per second and a split ratio of 1:20. The column is maintained at 40° for the first 12 minutes after an injection is made and is increased from 40° to 240° from 12 to 32 minutes after injection. During the period of 32 to 42 minutes after an injection is made the column is maintained at 240°. The injector port is maintained at 200°.

Procedure—Inject about 1.0 µL of *Standard solution B* into a suitable gas chromatograph, and record the chromatogram. The resolution, *R,* between the first major peak (acetaldehyde) and the second major peak (methanol) is not less than 1.5. Separately inject equal volumes (1.0 µL) of *Test solution A* and *Test solution B* into the chromatograph, record the chromatograms, and measure the major peaks. Calculate the concentration of methanol in *Test solution A:* not more than half the area of the corresponding peak in the chromatogram obtained with *Standard solution A* (200 ppm).

Calculate the sum of the contents of acetaldehyde and acetal, expressed as acetaldehyde, using the following expression:

$$[(10 \times A_E)/(A_T - A_E)] + [(30 \times C_E)/(C_T - C_E)],$$

where A_E is the area of the acetaldehyde peak in the chromatogram obtained with the *Test solution A;* A_T is the area of the acetaldehyde peak in the chromatogram obtained with *Standard solution B;* C_E is the area of the acetal peak in the chromatogram obtained with *Test solution A;* and C_T is the area of the acetal peak in the chromatogram obtained with *Standard solution C:* not more than 10 ppm, expressed as acetaldehyde.

Calculate the content of benzene using the following expression:

$$(2B_E)/(B_T - B_E),$$

where B_E is the area of the benzene peak in the chromatogram obtained with *Test solution A;* and B_T is the area of the benzene peak in the chromatogram obtained with *Standard*

solution D: not more than 2 ppm. If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

The total of all other impurities in the chromatogram obtained with *Test solution B:* not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with *Test solution B* (300 ppm).

Disregard any peaks that are 0.03 times the area of the peak corresponding to 4-methylpentan-2-ol in the chromatogram obtained with *Test solution B* (9 ppm).

Limit of nonvolatile residue—Evaporate 100 mL in a tared dish on a water bath, and dry at 100° to 105° for 1 hour: the weight of the residue does not exceed 2.5 mg.

BRIEFING

Dehydrated Alcohol, *USP 26* page 60. The European Pharmacopoeia is the coordinating pharmacopoeia for the international harmonization of compendial standards for the *Dehydrated Alcohol* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **ADOPTION Stage 6** document, is based in part on comments from the Japanese Pharmacopoeia and the United States Pharmacopeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the European Pharmacopoeia. Differences between the **ADOPTION Stage 6** document and the current *USP* monograph include the following:

(1) Definition—No change.
(2) *Packaging and storage*—Storage conditions to protect from light are added.
(3) *USP Reference standards*—A reference standard for Alcohol is added for the *Identification* test.
(4) *Identification*—Tests A and B are replaced with a more definitive *Infrared absorption* test, and the test for *Specific gravity* is moved under *Identification*.
(5) *Clarity of solution*—This test is added to comply with EP standards.
(6) *Color of solution*—This test is added to comply with EP standards.
(7) *Specific gravity*—No change.
(8) *Acidity*—This test is replaced by a test for *Acidity or alkalinity* to comply with EP standards.
(9) *Limit of nonvolatile residue*—The sample size is increased from 40 to 100 mL.
(10) *Water-insoluble substances*—This test is deleted. Because the monograph contains tests for *Nonvolatile residue* and *Volatile impurities,* this test is no longer needed.
(11) *Aldehydes and other foreign organic substances*—This test is replaced with a *Volatile impurities* test.
(12) *Amyl alcohol and nonvolatile, carbonizable substances*—This test is replaced with a *Volatile impurities* test.
(13) *Ultraviolet absorbance*—The standards have been modified to comply with EP standards.
(14) *Limit of acetone and isopropyl alcohol*—This test is replaced with a *Volatile impurities* test.
(15) *Methanol*—This test is replaced with a *Volatile impurities* test.
(16) *Volatile impurities*—This chromatographic test is added to limit a wide array of volatile impurities within a single test method.

(EMC: J. Lane) RTS—40108-1

Add the following:

Dehydrated Alcohol

C_2H_6O 46.07

Ethanol.

Ethyl alcohol [*64-17-5*].

» Dehydrated Alcohol contains not less than 99.2 percent, by weight, corresponding to not less that 99.5 percent, by volume, at 15.56°, of C_2H_5OH.

Packaging and storage—Preserve in tight containers, protected from light, remote from fire.

USP Reference standards ⟨11⟩—*USP Dehydrated Alcohol RS.*

Clarity of solution—[NOTE—*Test solution* is to be compared to *Reference suspension A* and to water in diffused daylight 5 minutes after preparation of *Reference suspension A.*]

Hydrazine solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Harmonization

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of *Hydrazine solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent* suspension to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension A.* Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension B.*

Test solution A—The substance to be examined.

Test solution B—Dilute 1.0 to 20 mL with water and allow to stand for 5 minutes before testing.

Procedure—Transfer a sufficient portion of *Test solution A* and *Test solution B* to separate test tubes of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A, Reference suspension B,* and water to separate, matching test tubes. Compare *Test solution A, Test solution B, Reference suspension A, Reference suspension B,* and water in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The diffusion of light must be such that *Reference suspension A* can readily be distinguished from water, and *Reference suspension B* can readily be distinguished from *Reference suspension A.*] *Test solution A* and *Test solution B* show the same clarity as that of water, or their opalescence is not more pronounced than that of *Reference suspension A.*

Color of solution—

Standard stock solution—Combine 3.0 mL ferric chloride CS, 3.0 mL cobaltous chloride CS, 2.4 mL cupric sulfate CS, and 1.6 mL dilute hydrochloric acid (10 g per L).

Standard solution—[NOTE—Prepare the *Standard solution* immediately before use.] Transfer 1.0 mL of *Standard stock solution* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix.

Test solution—The substance to be examined.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard solution* and water to separate matching test tubes. Compare the *Test solution, Standard solution,* and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* has the appearance of water or is not more intensely colored than the *Standard solution.*

Identification—

A: It complies with the test for *Specific gravity.*

B: *Infrared Absorption* ⟨197F⟩ or ⟨197S⟩ neat.

Specific gravity ⟨841⟩:not more than 0.7962 at 15.56°, indicating not less than 99.2% of C_2H_5OH, by weight.

Acidity or alkalinity—To 20 mL of alcohol, add 20 mL of freshly boiled and cooled water and 0.1 mL of *Phenolphthalein solution.* The solution is colorless. Add 1.0 mL of 0.01 N sodium hydroxide. The solution is pink (30 ppm, expressed as acetic acid).

Phenolphthalein solution—Dissolve 0.1 g of phenolphthalein in 80 mL of alcohol and dilute to 100 mL with water.

Ultraviolet absorption—Record the UV absorption spectrum of the test material from 200 to 400 nm in a 1-cm cell: maximum absorbance 0.40 at 240 nm, 0.30 between 250 and 260 nm, and 0.10 between 270 and 340 nm. Examine between 235 and 340 nm, in a 5-cm cell, using water as the compensation liquid. The absorption curve is smooth.

Volatile impurities—

Test solution A—The substance to be examined.

Test solution B—Add 150 µL of 4-methylpentan-2-ol to 500.0 mL of the substance to be examined.

Standard solution A—Dilute 100 µL of methanol to 50.0 mL with the substance to be examined. Dilute 5.0 mL of the solution to 50.0 mL with the substance to be examined.

Standard solution B—Dilute 50 µL of methanol and 50 µL of acetaldehyde to 50.0 ml with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

Standard solution C—Dilute 150 µL of acetal to 50.0 mL with the substance to be examined. Dilute 100 µL of the solution to 10.0 mL with the substance to be examined.

Standard solution D—Dilute 100 µL of benzene to 100.0 mL with the substance to be examined. Dilute 100 µL of the solution to 50.0 mL with the substance to be examined.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame ionization detector, maintained at about 280°, and a 0.32-mm × 30-m fused silica capillary column bonded with a 1.8 µm layer of phase G43. The carrier gas is helium with a linear velocity of about 35 cm per second and a split ratio of 1:20. The column is maintained at 40° for the first 12 minutes after an injection is made and is increased from 40° to 240° from 12 to 32 minutes after injection. During the period of 32 to 42 minutes after an injection is made the column is maintained at 240°. The injector port is maintained at 200°.

Procedure—Inject about 1.0 µL of *Standard solution B* into a suitable gas chromatograph, and record the chromatogram. The resolution, *R*, between the first major peak (acetaldehyde) and the second major peak (methanol) is not less than 1.5. Separately inject equal volumes (1.0 µL) of *Test solution A* and *Test solution B* into the chromatograph, record the chromatograms, and measure the major peaks. Calculate the concentration of methanol in *Test solution A:* not more than half the area of the corresponding peak in the chromatogram obtained with *Standard solution A* (200 ppm).

Calculate the sum of the contents of acetaldehyde and acetal, expressed as acetaldehyde, using the following expression:

$$[(10 \times A_E)/(A_T - A_E)] + [(30 \times C_E)/(C_T - C_E)],$$

where A_E is the area of the acetaldehyde peak in the chromatogram obtained with the *Test solution,* A_T is the area of the acetaldehyde peak in the chromatogram obtained with *Standard solution B,* C_E is the area of the acetal peak in the chromatogram obtained with *Test solution A,* and C_T is the area of the acetal peak in the chromatogram obtained with *Standard solution C:* not more than 10 ppm, expressed as acetaldehyde.

Calculate the content of benzene using the following expression:

$$(2B_E)/(B_T - B_E),$$

where B_E is the area of the benzene peak in the chromatogram obtained with *Test solution A,* and B_T is the area of the benzene peak in the chromatogram obtained with *Standard*

solution D: not more than 2 ppm. If necessary, the identity of benzene can be confirmed using another suitable chromatographic system (stationary phase with a different polarity).

The total of all other impurities in the chromatogram obtained with *Test solution B:* not more than the area of the peak due to 4-methylpentan-2-ol in the chromatogram obtained with *Test solution B* (300 ppm).

Disregard any peaks that are 0.03 times the area of the peak corresponding to 4-methylpentan-2-ol in the chromatogram obtained with *Test solution B* (9 ppm).

Limit of nonvolatile residue—Evaporate 100 mL in a tared dish on a water bath, and dry at 100° to 105° for 1 hour: the weight of the residue does not exceed 2.5 mg.

BRIEFING

Saccharin Calcium, *USP 26* page 1656. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Saccharin Calcium* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **Adoption Stage 6** document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

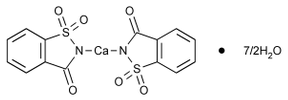
Differences between the Adoption Stage 6 document and the current USP monograph include the following:

(1) In the opening paragraph (the Definition)—The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
(2) *Packaging and storage*—Storage conditions are added.
(3) *Labeling*—No change.
(4) *USP Reference standards*—A reference standard for Saccharin Calcium is added for use in *Identification* test *A.*
(5) *Clarity of solution*—This test is added to comply with EP standards.
(6) *Color of solution*—This test is added to comply with EP standards.
(7) *Identification—Identification* tests *A, B,* and *D* are replaced with a more definitive IR absorption test. *Identification* test *C* is retained, but separated into 2 tests (*B* and *C*).
(8) *Water*—No change.
(9) *Readily carbonizable substances*—No change.
(10) *Selenium*—This test is deleted because it is unnecessary for this compound.
(11) *Limit of toluenesulfonamides*—The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method.
(12) *Heavy metals*—No change.
(13) *Limit of benzoate and salicylate*—No change.
(14) *Organic volatile impurities*—No change.
(15) *Assay*—No change.

(EMC: J. Lane) RTS—40107-1

Add the following:

Saccharin Calcium



$C_{14}H_8CaN_2O_6S_2 \cdot 3½H_2O$ 467.49

1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, calcium salt, hydrate (2:7)

1,2-Benzisothiazolin-3-one 1,1-dioxide calcium salt hydrate (2:7) [*6381-91-5*]

Anhydrous 404.44 [*6485-34-3*].

» Saccharin Calcium contains not less than 99.0 percent and not more than 101.0 percent of $C_{14}H_8CaN_2O_6S_2$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

Labeling—Where the quantity of saccharin calcium is indicated in the labeling of any preparation containing Saccharin Calcium, this shall be expressed in terms of saccharin ($C_7H_5NO_3S$).

USP Reference standards ⟨11⟩**—***USP Saccharin Calcium RS. USP o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.*

Clarity of solution—[NOTE—*Test solution* is to be compared to the *Reference suspension A* and to water in diffused daylight 5 minutes after preparation of *Reference suspension A.*]

Hydrazine solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of *Hydrazine solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension A.* Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension B.*

Test solution—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with water to 25 mL, and mix.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A, Reference suspension B,* water and a 200 g per L solution of sodium acetate to separate matching test tubes. Compare the *Test solution, Reference suspension A, Reference suspension B,* water, and a 200 g per L solution of sodium acetate in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The diffusion of light must be such that *Reference suspension A* can readily be distinguished from water, and that *Reference suspension B* can readily be distinguished from *Reference suspension A.*] The *Test solution* shows the same clarity as that of water, or the 200 g per L solution of sodium acetate, or its opalescence is not more pronounced that that of *Reference suspension A.*

Color of solution—

Standard stock solution—Combine 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, 2.4 mL of cupric sulfate CS, and 1.6 mL of dilute hydrochloric acid (10 g per L).

Standard solution—[NOTE—Prepare the *Standard solution* immediately before use.] Transfer 1.0 mL of *Standard stock solution* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix.

Test solution—Use the *Test solution* from *Clarity of solution.*

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard solution,* a 200 g per L solution of sodium acetate, and water to separate matching test tubes. Compare the *Test solution,* the *Standard solution,* a 200 g per L solution of sodium acetate, and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The

Test solution has the appearance of water or the 200 g per L solution of sodium acetate, or is not more intensely colored than the *Standard solution.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—Dry the specimen at 105° for 2 hours before use.

B: To a solution (1 in 10) add 2 drops of methyl red TS, and neutralize with 6 N ammonium hydroxide. Add 3 N hydrochloric acid, dropwise, until the solution is acid to the indicator. Upon the addition of ammonium oxalate TS, a white precipitate is formed. This precipitate is insoluble in 6 N acetic acid but dissolves in hydrochloric acid.

C: Calcium salts moistened with hydrochloric acid impart a transient yellowish red color to a nonluminous flame.

Water, *Method I* ⟨921⟩: not more than 15.0%.

Readily carbonizable substances ⟨271⟩**—**Dissolve 200 mg in 5 mL of sulfuric acid (between 94.5% and 95.5% [w/w] of H_2SO_4), and keep at a temperature of 48° to 50° for 10 minutes: the solution has no more color than *Matching Fluid A,* when viewed against a white background.

Heavy metals, *Method I* ⟨231⟩—Dissolve 4 g in 46 mL of water, add 4 mL of dilute hydrochloric acid (1 in 12), mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then pass through a dry filter, discarding the first 10 mL of the filtrate, and use 25 mL of the subsequent filtrate for the *Test Preparation:* the limit if 0.001%.

Limit of toluenesulfonamides—

Internal standard solution—Dissolve 25 mg of caffeine in methylene chloride, and dilute with the same solvent to 100 mL.

Reference solution—Dissolve 20.0 mg of USP *o*-Toluenesulfonamide RS and 20.0 mg of USP *p*-Toluenesulfonamide RS in methylene chloride, and dilute with the same solvent to 100.0 mL. Dilute 5.0 mL of the solution with methylene chloride to 50.0 mL. Evaporate 5.0 mL of the final solution to dryness in a stream of nitrogen. Dissolve the residue in 1.0 mL of the *Internal standard solution.*

Test solution—Suspend 10.0 g of the substance to be examined in 20 mL of water, and dissolve using 5 mL to 6 mL of 1 N sodium hydroxide. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to pH 7 to 8, and dilute with water to 50 mL. Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding 40°. Using a small quantity of methylene chloride, quantitatively transfer the residue into a suitable 10-mL tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the *Internal standard solution.*

Blank solution—Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding 40°. Dissolve the residue in 1 mL of methylene chloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The instrument is equipped with a flame-ionization detector and contains a fused silica column 10 m long and 0.53 mm in internal diameter, coated with G3 phase (film thickness 2 μm). The injector port, column, and detector are maintained at temperatures of about 250°, 180°, and 250°, respectively, and nitrogen is used as the carrier gas at a flow rate of about 10 mL per minute. The injector employs a split ratio of 1:2.

Procedure—Inject about 1 µL of the *Reference solution.* Adjust the sensitivity of the detector so that the height of the peak due to caffeine is not less than 50% of the full scale of the recorder. The substances are eluted in the following order: *o*-toluenesulfonamide, *p*-toluenesulfonamide, and caffeine. The test is not valid unless the resolution between the peaks due to *o*-toluenesulfonamide and *p*-toluenesulfonamide is at least 1.5. Inject about 1 µL of the *Blank solution.* In the chromatogram obtained, verify that there are no peaks with the same retention times as the internal standard, *o*-toluenesulfonamide and *p*-toluenesulfonamide. Inject about 1 µL of the *Test solution* and 1 µL of the *Reference solution.* If any peaks due to *o*-toluenesulfonamide and *p*-toluenesulfonamide appear in the chromatogram obtained with the *Test solution,* the ratio of their areas to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the *Reference solution* (10 ppm of *o*-toluenesulfonamide and 10 ppm of *p*-toluenesulfonamide).

Limit of benzoate and salicylate—To 10 mL of a solution (1 in 20), previously acidified with 5 drops of 6 N acetic acid, add 3 drops of ferric chloride TS: no precipitate or violet color appears.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Assay—Dissolve, with the aid of slight heating if necessary, about 150 mg of Saccharin Calcium, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N perchloric acid is equivalent to 20.22 mg of $C_{14}H_8CaN_2O_6S_2$.

BRIEFING

Saccharin Sodium, *USP 26* page 1657. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Saccharin Sodium* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **Adoption Stage 6** document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

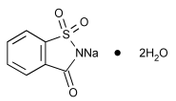
Differences between the Adoption Stage 6 document and the current USP monograph include the following:

(1) In the opening paragraph (the Definition)—The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
(2) *Packaging and storage*—Storage conditions are added.
(3) *Labeling*—No change.
(4) *USP Reference standards*—A reference standard for Saccharin Sodium is added for use in *Identification A* test.
(5) *Clarity of solution*—This test is added to comply with EP standards.
(6) *Color of solution*—This test is added to comply with EP standards.
(7) *Identification—Identification* tests *A, B,* and *D* are replaced with a more definitive IR test. *Identification* test *C* is retained, but separated into 2 tests (*B* and *C*).
(8) *Water*—No change.
(9) *Readily carbonizable substances*—No change.
(10) *Selenium*—This test is deleted because it is unnecessary for this compound.
(11) *Limit of toluenesulfonamides*—The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method.
(12) *Heavy metals*—No change.
(13) *Limit of benzoate and salicylate*—No change.
(14) *Organic volatile impurities*—No change.
(15) *Assay*—No change.

(EMC: J. Lane) RTS—40105-1

Add the following:

Saccharin Sodium



$C_7H_4NNaO_3S \cdot 2H_2O$ 241.20

1,2-Benzisothiazol-3(2H)-one, 1,1-dioxide, sodium salt, dihydrate.

1,2-Benzisothiazolin-3-one 1,1-dioxide sodium salt dihydrate [*6155-57-3*].

Anhydrous 205.17 [*128-44-9*].

Harmonization

» Saccharin Sodium contains not less than 99.0 percent and not more than 101.0 percent of $C_7H_4NNaO_3S \cdot 2H_2O$, calculated on the anhydrous basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

Labeling—Where the quantity of saccharin sodium is indicated in the labeling of any preparation containing Saccharin Sodium, this shall be expressed in terms of saccharin ($C_7H_5NO_3S$).

USP Reference standards ⟨11⟩**—***USP Saccharin Sodium RS. USP o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.*

Clarity of solution—[NOTE—The *Test solution* is to be compared to the *Reference suspension A* and to water in diffused daylight 5 minutes after preparation of *Reference suspension A.*]

Hydrazine solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of *Hydrazine solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension A*. Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension B.*

Test solution—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with water to 25 mL, and mix.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A, Reference suspension B,* water and a 200 g per L solution of sodium acetate to separate matching test tubes. Compare the *Test solution, Reference suspension A, Reference suspension B,* water, and a 200 g per L solution of sodium acetate in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The diffusion of light must be such that *Reference suspension A* can readily be distinguished from water, and that *Reference suspension B* can readily be distinguished from *Reference suspension A.*] The *Test solution* shows the same clarity as that of water, or the 200 g per L solution of sodium acetate, or its opalescence is not more pronounced that that of *Reference suspension A.*

Color of solution—

Standard stock solution—Combine 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, 2.4 mL cupric sulfate CS, and 1.6 mL of dilute hydrochloric acid (10 g per L).

Standard solution—[NOTE—Prepare the *Standard solution* immediately before use.] Transfer 1.0 mL of *Standard stock solution* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix.

Test solution—Use the *Test solution* from *Clarity of solution.*

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard solution,* a 200 g per L solution of sodium acetate, and water to separate matching test tubes. Compare the *Test solution,* the *Standard solution,* a 200 g per L solution of sodium acetate, and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* has the appearance of water or the 200 g per L solution of sodium acetate, or is not more intensely colored than the *Standard solution.*

Identification—

A: *Infrared Absorption* ⟨197K⟩—Dry the specimen at 105° for 2 hours before use.

B: To a solution (1 in 10) add 2 mL of 15% potassium carbonate, and heat to boiling. No precipitate is formed. Add 4 mL of potassium pyroantimonate TS, and heat to boiling. Allow to cool in ice water and, if necessary, rub the inside of the test tube with a glass rod. A dense precipitate is formed.

C: Sodium salts impart an intense yellow color to a nonluminous flame.

Acidity or alkalinity—To a solution of 1.0 g in 10 mL of carbon dioxide-free water add 1 drop of phenolphthalein TS: no pink color is produced. Then add 1 drop of 0.1 N sodium hydroxide: a pink color is produced.

Water, *Method I* ⟨921⟩: not more than 15.0%.

Readily carbonizable substances ⟨271⟩—Dissolve 200 mg in 5 mL of sulfuric acid (between 94.5% and 95.5% [w/w] of H_2SO_4), and keep at a temperature of 48° to 50° for 10 minutes: the solution has no more color than *Matching Fluid A,* when viewed against a white background.

Heavy metals, *Method I* ⟨231⟩—Dissolve 4 g in 46 mL of water, add 4 mL of dilute hydrochloric acid (1 in 12), mix, and rub the inner wall of the vessel with a glass rod until crystallization begins. Allow the solution to stand for 1 hour, then pass through a dry filter, discarding the first 10 mL of the filtrate, and use 25 mL of the subsequent filtrate for the *Test Preparation:* the limit is 0.001%.

Limit of toluenesulfonamides—

Internal standard solution—Dissolve 25 mg of caffeine in methylene chloride, and dilute with the same solvent to 100 mL.

Reference solution—Dissolve 20.0 mg of USP *o*-Toluenesulfonamide RS and 20.0 mg of USP *p*-Toluenesulfonamide RS in methylene chloride, and dilute with the same solvent to 100.0 mL. Dilute 5.0 mL of the solution with methylene chloride to 50.0 mL. Evaporate 5.0 mL of the final solution to dryness in a stream of nitrogen. Dissolve the residue in 1.0 mL of the *Internal standard solution.*

Test solution—Suspend 10.0 g of the substance to be examined in 20 mL of water, and dissolve using 5 mL to 6 mL of 1 N sodium hydroxide. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to pH 7 to 8 and dilute with water to 50 mL. Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding 40°. Using a small quantity of methylene chloride, quantitatively transfer the residue

into a suitable 10-mL tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the *Internal standard solution.*

Blank solution—Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding 40°. Dissolve the residue in 1 mL of methylene chloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The instrument is equipped with a flame-ionization detector and contains a fused silica column 10 m long and 0.53 mm in internal diameter, coated with G3 phase (film thickness 2 µm). The injector port, column, and detector are maintained at temperatures of about 250°, 180°, and 250°, respectively, and nitrogen is used as the carrier gas at a flow rate of about 10 mL per minute. The injector employs a split ratio of 1:2.

Procedure—Inject about 1 µL of the *Reference solution.* Adjust the sensitivity of the detector so that the height of the peak due to caffeine is not less than 50% of the full scale of the recorder. The substances are eluted in the following order: *o*-toluenesulfonamide, *p*-toluenesulfonamide, and caffeine. The test is not valid unless the resolution between the peaks due to o-toluenesulfonamide and *p*-toluenesulfonamide is at least 1.5. Inject about 1 µL of the *blank solution.* In the chromatogram obtained, verify that there are no peaks with the same retention times as the internal standard, *o*-toluenesulfonamide and *p*-toluenesulfonamide. Inject about 1 µL of the *Test solution* and 1 µL of the *Reference solution.* If any peaks due to *o*-toluenesulfonamide and *p*-toluenesulfonamide appear in the chromatogram obtained with the test solution, the ratio of their areas to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the *Reference solution* (10 ppm of *o*-toluenesulfonamide and 10 ppm of *p*-toluenesulfonamide).

Limit of benzoate and salicylate—To 10 mL of a solution (1 in 20), previously acidified with 5 drops of 6 N acetic acid, add 3 drops of ferric chloride TS: no precipitate or violet color appears.

Organic volatile impurities, *Method I* ⟨467⟩: meets the requirements.

Assay—Dissolve, with the aid of slight heating if necessary, about 150 mg of Saccharin Sodium, accurately weighed, in 50 mL of glacial acetic acid. Titrate with 0.1 N perchloric acid, determining the endpoint potentiometrically. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N perchloric acid is equivalent to 20.52 mg of $C_7H_4NNaO_3S$.

MONOGRAPHS (NF)

BRIEFING

Saccharin, *NF 21* page 2825. The United States Pharmacopeia is the coordinating pharmacopeia for the international harmonization of the compendial standards for the *Saccharin* monograph, as part of the process of international harmonization of monographs and general analytical methods of the European, Japanese, and United States pharmacopeias. The following monograph, which represents the **Adoption Stage 6** document, is based in part on comments from the Japanese Pharmacopoeia and the European Pharmacopoeia in response to the Provisional Harmonized Text Stage 5A and 5B drafts prepared by the United States Pharmacopeia.

Differences between the Adoption Stage 6 document and the current *NF* monograph include the following:

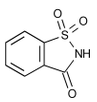
(1) In the opening paragraph (the Definition)—The lower limit is changed from not less than 98.0 percent to not less than 99.0 percent.
(2) *Packaging and storage*—Storage conditions are added.
(3) *USP Reference standards*—A reference standard for Saccharin is added for use in the *Identification* test.
(4) *Clarity of solution*—This test is added to comply with EP standards.
(5) *Color of solution*—This test is added to comply with EP standards.
(6) *Identification—Identification* tests *A* and *B* are replaced with a more definitive IR absorption test.
(7) *Melting range*—No change.

(8) *Loss on drying*—No change.
(9) *Readily carbonizable substances*—No change.
(10) *Residue on ignition*—No change.
(11) *Limit of toluenesulfonamides*—The test method and limits are changed to those of the European Pharmacopoeia, which include a more modern test method.
(12) *Selenium*—This test is deleted because it is unnecessary for this compound.
(13) *Heavy metals*—No change.
(14) *Limit of benzoate and salicylate*—No change.
(15) *Organic volatile impurities*—No change.
(16) *Assay*—No change.

(EMC: J. Lane) RTS—40106-1

Add the following:

Saccharin



$C_7H_5NO_3S$ 183.19

1,2-Benzisothiazol-3(*2H*)-one, 1,1-dioxide.

1,2-Benzisothiazolin-3-one 1,1-dioxide [*81-07-2*].

» Saccharin contains not less than 99.0 percent and not more than 101.0 percent of $C_7H_5NO_3S$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. Store at room temperature.

USP Reference standards ⟨11⟩**—***USP Saccharin RS. USP o-Toluenesulfonamide RS. USP p-Toluenesulfonamide RS.*

Clarity of solution—[NOTE—The *Test solution* is to be compared to the *Reference suspension A* and to water in diffused daylight 5 minutes after preparation of *Reference suspension A.*]

Hydrazine solution—Transfer 1.0 g of hydrazine sulfate to a 100-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Allow to stand for 4 to 6 hours.

Methenamine solution—Transfer 2.5 g of methenamine to a 100-mL glass-stoppered flask, add 25.0 mL of water, insert the glass stopper, and mix to dissolve.

Primary opalescent suspension—[NOTE—This suspension is stable for 2 months, provided it is stored in a glass container free from surface defects. The suspension must not adhere to the glass and must be well mixed before use.] Transfer 25.0 mL of *Hydrazine solution* to the *Methenamine solution* in the 100-mL glass-stoppered flask. Mix, and allow to stand for 24 hours.

Opalescence standard—[NOTE—This suspension should not be used beyond 24 hours after preparation.] Transfer 15.0 mL of the *Primary opalescent suspension* to a 1000-mL volumetric flask, dilute with water to volume, and mix.

Reference suspensions—Transfer 5.0 mL of the *Opalescence standard* to a 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension A.* Transfer 10.0 mL of the *Opalescence standard* to a second 100-mL volumetric flask, dilute with water to volume, and mix to obtain *Reference suspension B.*

Test solution—Dissolve 5.0 g of test material in about 20 mL of a 200 g per L solution of sodium acetate, dilute with water to 25 mL, and mix.

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Reference suspension A, Reference suspension B,* water and a 200 g per L solution of sodium acetate to separate matching test tubes. Compare the *Test solution, Reference suspension A, Reference suspension B,* water, and a 200 g per L solution of sodium acetate in diffused daylight, viewing vertically against a black background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). [NOTE—The diffusion of light must be such that *Reference suspen-*

sion A can readily be distinguished from water, and that *Reference suspension B* can readily be distinguished from *Reference suspension A.*] The *Test solution* shows the same clarity as that of water, or the 200 g per L solution of sodium acetate, or its opalescence is not more pronounced that that of *Reference suspension A.*

Color of solution—

Standard stock solution—Combine 3.0 mL of ferric chloride CS, 3.0 mL of cobaltous chloride CS, 2.4 mL of cupric sulfate CS, and 1.6 mL of dilute hydrochloric acid (10 g per L).

Standard solution—[NOTE—Prepare the *Standard solution* immediately before use.] Transfer 1.0 mL of *Standard stock solution* to a 100-mL volumetric flask, dilute with dilute hydrochloric acid (10 g per L) to volume, and mix.

Test solution—Use the *Test solution* from *Clarity of solution.*

Procedure—Transfer a sufficient portion of the *Test solution* to a test tube of colorless, transparent, neutral glass with a flat base and an internal diameter of 15 mm to 25 mm to obtain a depth of 40 mm. Similarly transfer portions of *Standard solution*, a 200 g per L solution of sodium acetate, and water to separate matching test tubes. Compare the *Test solution,* the *Standard solution,* a 200 g per L solution of sodium acetate, and water in diffused daylight, viewing vertically against a white background (see *Visual Comparison* under *Spectrophotometry and Light-Scattering* ⟨851⟩). The *Test solution* has the appearance of water or the 200 g per L solution of sodium acetate, or is not more intensely colored than the *Standard solution.*

Identification, *Infrared Absorption* ⟨197K⟩.

Melting range ⟨741⟩**:** between 226° and 230°.

Loss on drying ⟨731⟩—Dry it at 105° for 2 hours: it loses not more than 1.0% of its weight.

Readily carbonizable substances ⟨271⟩—Dissolve 200 mg in 5 mL of sulfuric acid (between 94.5% and 95.5% [w/w] of H_2SO_4), and keep at a temperature of 48° to 50° for 10 minutes: the solution has no more color than *Matching Fluid A,* when viewed against a white background.

Residue on ignition ⟨281⟩: not more than 0.2%. Ignition temperature: 600 ± 50°.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Limit of toluenesulfonamides—

Internal standard solution—Dissolve 25 mg of caffeine in methylene chloride, and dilute to 100 mL with the same solvent.

Reference solution—Dissolve 20.0 mg of USP *o*-Toluenesulfonamide RS and 20.0 mg of USP *p*-Toluenesulfonamide RS in methylene chloride, and dilute with the same solvent to 100.0 mL. Dilute 5.0 mL of the solution with methylene chloride to 50.0 mL. Evaporate 5.0 mL of the final solution to dryness in a current of nitrogen. Dissolve the residue in 1.0 mL of the *Internal standard solution.*

Test solution—Suspend 10.0 g of the substance to be examined in 20 mL of water, and dissolve using 5 mL to 6 mL of 1 N sodium hydroxide. If necessary adjust the solution with 1 N sodium hydroxide or 1 N hydrochloric acid to pH 7 to 8, and dilute to 50 mL with water. Shake the solution with four quantities each of 50 mL of methylene chloride. Combine the lower layers, dry over anhydrous sodium sulfate, and filter. Wash the filter and the sodium sulfate with 10 mL of methylene chloride. Combine the solution and the washings, and evaporate almost to dryness in a water bath at a temperature not exceeding 40°. Using a small quantity of methylene chloride, quantitatively transfer the residue into a suitable 10 mL tube, evaporate to dryness in a stream of nitrogen, and dissolve the residue in 1.0 mL of the *Internal standard solution.*

Blank solution—Evaporate 200 mL of methylene chloride to dryness in a water bath at a temperature not exceeding 40°. Dissolve the residue in 1 mL of methylene chloride.

Chromatographic system (see *Chromatography* ⟨621⟩)—The instrument is equipped with a flame-ionization detector and contains a fused silica column 10 m long and 0.53 mm in internal diameter, coated with G3 phase (film thickness 2 µm). The injector port, column, and detector are maintained at temperatures of about 250°, 180°, and 250°, respectively, and nitrogen is used as the carrier gas at a flow rate of about 10 mL per minute. The injector employs a split ratio of 1:2.

Procedure—Inject about 1 µL of the *Reference solution.* Adjust the sensitivity of the detector so that the height of the peak due to caffeine is not less than 50% of the full scale of the recorder. The substances are eluted in the following order: *o*-toluenesulfonamide, *p*-toluenesulfonamide, and caffeine. The test is not valid unless the resolution between the peaks due to *o*-toluenesulfonamide and *p*-toluenesulfonamide is at least 1.5. Inject about 1 µL of the *Blank solution.* In the chromatogram obtained, verify that there are no peaks with the same retention times as the internal standard, *o*-toluenesulfonamide, and *p*-toluenesulfonamide. Inject about 1 µL of the *Test solution* and 1 µL of the *Reference solution.* If any peaks due to *o*-toluenesulfonamide, and *p*-toluenesulfonamide appear in the chromatogram obtained with the *Test solution,* the ratio of their areas to that of the internal standard is not greater than the corresponding ratio in the chromatogram obtained with the *Reference solution* (10 ppm of *o*-toluenesulfonamide and 10 ppm of *p*-toluenesulfonamide).

Limit of benzoate and salicylate—To 10 mL of a hot, saturated solution of it add ferric chloride TS, dropwise: no precipitate or violet color appears in the liquid.

Organic volatile impurities, *Method V* ⟨467⟩: meets the requirements.

Solvent—Use dimethyl sulfoxide as the solvent.

Assay—Accurately weigh about 500 mg of Saccharin, dissolve in 40 mL of alcohol, add 40 mL of water, mix, add phenolphthalein TS, and titrate with 0.1 N sodium hydroxide. Perform a blank titration, if necessary, and make the appropriate correction. Each mL of 0.1 N sodium hydroxide is equivalent to 18.32 mg of $C_7H_5NO_3S$.

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**61**⟩ **Microbial Limit Tests,** *USP 26* page 2006. The proposed revision to this chapter, which includes a name change and which previously appeared as a Pharmacopeial Discussion Group (PDG) Stage 4 OFFICIAL INQUIRY (see page 2299 of *PF* 27(2) [Mar.–Apr. 2001]), has undergone extensive changes. Therefore the previous Stage 4 document is hereby canceled and replaced by this new PDG **Stage 4 OFFICIAL INQUIRY**. The following changes were based upon comments received in response to the previous Stage 4 document and upon discussions held by experts from the EP, JP, and USP:

(1) References to method "validation" have been replaced by the more appropriate terminology "verification of suitability of the method".
(2) The section describing preparation of test strains has been modified in order to allow more flexibility (e.g., use of commercial strains instead of freshly prepared strains; use of solid as well as liquid agar to grow bacterial strains; use of Sabouraud-Dextrose Medium for *Candida albicans;* use of Potato Dextrose Agar Medium for growth of *Aspergillus niger;* use of stable spore suspensions; and storage of the test organism suspension for up to 24 hours.)
(3) The sections on growth promotion have been significantly expanded (e.g., indications of which microorganism grows on which medium, incubation conditions). Criteria for liquid media have been added. In the tests for specified microorganisms, a new section for verification of the selectivity of the

media has been introduced; the verification of the suitability of the medium is carried out with separate microorganism suspensions.
(4) More detailed instructions on how to cope with products containing antimicrobial agents have been added throughout the texts. In particular, growth is considered inhibited if there is a reduction by a factor of 2 (0.3 log).
(5) Confidence limits for the most-probable-number (MPN) method have been added.
(6) Regarding interpretation of the results, clarification has been made with regard to the counting of colonies.

Other changes of lesser significance have been made throughout the text. Comments regarding this Stage 4 proposal are invited and should be submitted by **31 October 2003**.

(AMB: D. Porter) RTS—40088-1

Add the following:

⟨61⟩ MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: MICROBIAL ENUMERATION TESTS

INTRODUCTION

The tests described hereafter will allow quantitative enumeration of mesophilic bacteria and fungi that may grow under aerobic conditions. [NOTE—See *Buffer Solutions and Media* in the general test chapter *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩ for preparation of the solutions and media used in this chapter.]

The tests are designed primarily to determine whether a substance or preparation complies with an established specification for microbiological quality. When used for such purposes, follow the instructions given below, including the number of samples to be taken, and interpret the results as stated below.

The methods are not applicable to products containing viable microorganisms as active ingredients.

Alternative microbiological procedures, including automated methods, may be used, provided that their equivalence to the Pharmacopeial method has been demonstrated.

GENERAL PROCEDURES

Carry out the determination under conditions designed to avoid extrinsic contamination of the product to be examined. The precautions taken to avoid contamination must be such that they do not affect any microorganisms that are to be revealed in the test.

If the product to be examined has antimicrobial activity, this is, insofar as possible, removed or neutralized. If inactivators are used for this purpose, their efficacy and their absence of toxicity for microorganisms must be demonstrated.

If surface-active substances are used for sample preparation, their absence of toxicity for microorganisms and their compatibility with any inactivators used must be demonstrated.

ENUMERATION METHODS

Use the *Membrane Filtration Method* or the one of the *Plate-Count Methods*, as directed below. The *Most-Probable-Number (MPN) Method* is generally the least accurate method for microbial counts; however, for certain product groups with very low bioburden, it may be the most appropriate method.

The choice of a method is based on factors such as the nature of the product and the required limit of microorganisms. The method chosen must allow testing of a sufficient sample size to judge compliance with the specification, and the suitability of the chosen method must be established.

GROWTH PROMOTION TEST AND SUITABILITY OF THE COUNTING METHOD

General Considerations

The ability of the test to detect microorganisms in the presence of product must be established.

Suitability must be confirmed if a change in testing performance or in the product, which may affect the outcome of the test, is introduced.

Preparation of Test Strains

Use standardized stable suspensions, or prepare as stated below. Seed-lot culture maintenance techniques (seed-lot systems) are used so that the viable microorganisms used for inoculation are not more than five passages removed from the original master seed-lot. Grow the bacterial test strains separately in containers containing *Soybean–Casein Digest Medium* or *Soybean–Casein Digest Agar Medium* for 18 to 24 hours between 30° and 35°. Grow the fungal test strains separately on *Sabouraud Dextrose Agar Medium* for both fungi or *Potato Dextrose Agar Medium* for *Aspergillus niger* and *Sabouraud Dextrose Medium* for *Candida albicans* for 2 to 3 days between 20° and 25° and for 5 to 7 days between 20° and 25° for *Aspergillus niger.*

Staphylococcus aureus	such as ATCC 6538, NCIMB 9518, CIP 4.83, or NBRC 13276
*Pseudomonas aeruginos*a	such as ATCC 9027, NCIMB 8626, CIP 82.118, or NBRC 13275
Bacillus subtilis	such as ATCC 6633, NCIMB 8054, CIP 52.62, or NBRC 3134
Candida albicans	such as ATCC 10231, NCPF 3179, IP 48.72, or NBRC 1594
Aspergillus niger	such as ATCC 16404, IMI 149007, IP 1431.83, or NBRC 9455

Use *pH 7.0 Buffered Sodium Chloride–Peptone Solution* or *pH 7.2 Phosphate Buffer* to make suitable test suspensions; to suspend *A. niger* spores, 0.05% of polysorbate 80 may be added to the buffer. Use the suspensions within 2 hours, or within 24 hours if stored between 2° and 8°. As an alternative to preparing and then diluting a fresh suspension of vegetative cells of *A. niger* or *B. subtilis,* a stable spore suspension is prepared and then an appropriate volume of the spore suspension is used for test inoculation. The stable spore suspension may be maintained at 2° to 8° for a validated period of time.

Negative Control

To verify the absence of contamination in media a portion of each batch is incubated. To verify testing conditions, a negative control is performed using the chosen diluent as the test preparation for each batch of diluent. There must be no growth of microorganisms.

Growth Promotion of the Media

Test each batch of ready-prepared medium and each batch of medium prepared either from dehydrated medium or from ingredients (see *Buffer Solutions and Media* under *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms* ⟨62⟩. In appropriate cases, periodic testing of the different batches prepared from the same lot of dehydrated medium is acceptable.

Inoculate portions of *Soybean–Casein Digest Medium* and *Soybean–Casein Digest Agar Medium* with a small number (not more than 100 cfu) of the following microorganisms, using a separate portion or plate of medium for each: *Bacillus subtilis, Pseudomonas aeruginosa, Staphylococcus aureus, Aspergillus niger* (agar medium only), *Candida albicans* (agar medium only). Inoculate plates of *Sabouraud Dextrose Agar Medium* with a small number

(not more than 100 cfu) of *Aspergillus niger* and *Candida albicans,* using a separate plate of medium for each. Incubate at the specified temperature for not more than 3 days in the case of bacteria and not more than 5 days in the case of fungi.

For solid media, growth obtained must not differ by a factor greater than 2 (0.3 log) from the calculated value for the inoculum determined on a previously used batch of medium and must show growth characteristics comparable to a previously used batch of medium. Liquid media are suitable if clearly visible growth of the microorganisms occurs comparable to a previously used batch of medium.

Suitability of the Counting Method

PREPARATION OF THE SAMPLE

The method for sample preparation depends on the physical characteristics of the product to be tested. If none of the procedures described below can be demonstrated to be satisfactory, a suitable alternative procedure must be developed.

Water-Soluble Products—Dissolve or dilute (usually a 1 in 10 dilution is prepared) the product to be examined in *pH 7.0 Buffered Sodium Chloride–Peptone Solution, pH 7.2 Phosphate Buffer,* or *Soybean–Casein Digest Medium*. If necessary adjust to a pH of 6 to 8. Further dilutions, where necessary, are prepared with the same diluent.

Nonfatty Products Insoluble in Water—Suspend the product to be examined (usually a 1 in 10 dilution is prepared) in *pH 7.0 Buffered Sodium Chloride–Peptone Solution , pH 7.2 Phosphate Buffer,* or *Soybean–Casein Digest Medium*. A suitable surface-active agent such as 1 g per L of polysorbate 80 may be added to assist the suspension of poorly wettable substances. If necessary, adjust to a pH of 6 to 8. Further dilutions, where necessary, are prepared with the same diluent.

Fatty Products—Dissolve in isopropyl myristate sterilized by filtration, or homogenize the product to be examined with the minimum necessary quantity of sterile polysorbate 80 or another suitable sterile surface-active reagent, heated if necessary to not more than 40°—or in exceptional cases to not more than 45°. Mix carefully, and if necessary maintain the temperature in a water bath. Add a sufficient amount of the prewarmed chosen diluent to make a 1 in 10 dilution of the original product. Mix carefully while maintaining the temperature for the shortest time necessary until an emulsion is formed. Further serial 10-fold dilutions may be prepared using the chosen diluent containing a suitable concentration of sterile polysorbate 80 or another suitable sterile surface-active reagent.

Fluids or Solids in Aerosol Form—Aseptically transfer the product into a membrane filter apparatus, or a suitable sterile container, for further sampling. Use either the total contents or a defined number of metered doses from each of the containers tested.

Transdermal Patches—Remove the protective cover sheets (''release liners'') of the transdermal patches and place them, adhesive side upwards, on sterile glass or plastic trays. Cover the adhesive surface with a suitable sterile porous material to prevent the patches from sticking together, and transfer the patches to a suitable volume of the chosen diluent containing suitable inactivators such as polysorbate 80 or lecithin. Shake the preparation vigorously for at least 30 minutes.

INOCULATION AND DILUTION

Add to the sample, prepared as directed for *Preparation of the Sample,* a sufficient volume of the microbial suspension to obtain a final level of less than 100 cfu per mL. If inhibi-

tion of growth by the sample cannot otherwise be avoided, the aliquot of the microbial suspension may be added after neutralization, dilution, or filtration.

To demonstrate suitable microbial recovery from the product, the first possible dilution must be tested. Where this is not possible due to antimicrobial activity or poor solubility, further appropriate protocols must be developed.

NEUTRALIZATION AND REMOVAL OF ANTIMICROBIAL ACTIVITY

The number of microorganisms recovered from the incubated sample preparation is compared to the number of microorganisms recovered from the control preparation (no test material included). If growth is inhibited (reduction by a factor of 2, or 0.3 log or greater), then modify the procedure for the particular enumeration test to ensure the validity of the results. Modification of the procedure may include the following:

(1) an increase in the volume of the diluent,
(2) incorporation of suitable specific or general neutralizing agents into the diluent,
(3) membrane filtration, or
(4) a combination of the above measures.

Where neutralizers are used specifically to neutralize or to remove antimicrobial substances in a sample, the absence of toxicity for microorganisms of the neutralizer or inactivator, and any by-products of neutralization or inactivation, is demonstrated by carrying out a blank with neutralizer and without product.

Neutralizing Agents—Neutralizing agents may be used to neutralize the activity of antimicrobial agents (see *Table 1*). They may be added to the chosen diluent or to the medium, preferably before sterilization. If used, their efficacy and their absence of toxicity for microorganisms must be demonstrated.

Table 1. Common Neutralizing Agents for Interfering Substances

Interfering Substances	Potential Neutralizing Agent
Glutaraldehyde, mercurials	Bisulfate
Phenolics, alcohol, aldehydes, sorbate	Dilution
Aldehydes	Glycine
Quaternary ammonium compounds (QACs), Parahydroxy-benzoates (parabens), bis-biguanides	Lecithin
QAC, iodine, parabens	Polysorbate
Mercurials	Thioglycolate
Mercurials, halogens, aldehydes	Thiosulfate
EDTA (edetate)	Mg^{+2} or Ca^{+2} ions

If in spite of the incorporation of suitable inactivating agents and a substantial increase in the volume of diluent, it is still not possible to recover the viable cultures described above and if the article is not suitable for employment of membrane filtration, it can be assumed that the failure to isolate the inoculated organism is attributable to the bactericidal activity of the product. This information serves to indicate that the article is not likely to be contaminated with the given species of the microorganism. However, it is possible that the product inhibits some of the microorganisms specified herein but does not inhibit others not included among the test strains or for which the latter are not representative. Therefore, perform the test with the lowest possible dilution that gives acceptable recovery of the test microorganisms.

EXAMINATION OF THE SAMPLE

For each of the microorganisms listed, separate tests are performed.

Membrane Filtration—Use membrane filters having a nominal pore size not greater than 0.45 µm. The type of filter material is chosen in such a way that the bacteria-retaining efficiency is not affected by the components of the sample to be investigated. For each of the microorganisms listed, one membrane filter is used.

Transfer a suitable quantity of the sample prepared as described for *Inoculation and Dilution* and *Neutralization and Removal of Antimicrobial Activity* under *Preparation of the Sample,* preferably representing 1 g of the product—or less if large numbers of cfu are expected—to the membrane filter, filter immediately, and rinse the membrane filter with an appropriate volume of diluent.

For the determination of total aerobic microbial count (TAMC), transfer the membrane filter to the surface of the *Soybean–Casein Digest Agar Medium*. For the determination of total combined yeasts and molds count (TYMC), transfer the membrane to the surface of the *Sabouraud Dextrose Agar Medium.* Incubate the plate of *Soybean–Casein Digest Agar Medium* for not more than 3 days between 30° and 35° and the plate of *Sabouraud Dextrose Agar Medium* for not more than 5 days between 20° and 25°. Perform the counting.

Plate-Count Methods—Perform Plate-Count Methods at least in duplicate for each medium.

Pour-Plate Method—For Petri dishes 9 cm in diameter, add to the dish 1 mL of the sample prepared as described for *Inoculation and Dilution* and *Neutralization and Removal of Antimicrobial Activity* under *Preparation of the Sample* and 15 to 20 mL of *Soybean–Casein Digest Agar Medium*, or 15 to 20 mL of *Sabouraud Dextrose Agar Medium,* both media maintained at not more than 45°. If larger Petri dishes are used, the amount of agar medium is increased accordingly. For each of the microorganisms listed, at least two Petri dishes are used.

Incubate the plates of *Soybean–Casein Digest Agar Medium* for not more than 3 days between 30° and 35° and the plates of *Sabouraud Dextrose Agar Medium* for not more than 5 days between 20° and 25°. Take the arithmetic mean of the counts per medium, and calculate the number of cfu in the original inoculum.

Surface-Spread Method—For Petri dishes 9 cm in diameter, add 15 to 20 mL of *Soybean–Casein Digest Agar Medium* or *Sabouraud Dextrose Agar Medium* at about 45° to each Petri dish, and allow to solidify. If larger Petri dishes are used, the volume of the agar is increased accordingly. Dry the plates, for example, in a laminar-air-flow cabinet or in an incubator. For each of the microorganisms listed, at least two Petri dishes are used. Spread a measured volume of not less than 0.1 mL of the sample, prepared as directed for *Inoculation and Dilution* and *Neutralization and Removal of Antimicrobial Activity* under *Preparation of the Sample*, over the surface of the medium. Incubate, and count as directed for *Pour-Plate Method*.

Most-Probable-Number (MPN) Method—The precision and accuracy of the MPN Method is less than that of the *Membrane Filtration Method* or the *Plate-Count Method*. Unreliable results are obtained particularly for the enumeration of molds. For these reasons the MPN Method is reserved for the enumeration of microorganisms in situations where no other method is available. If the use of the method is justified, proceed as follows.

Prepare a series of at least three serial 10-fold dilutions of the product as described for *Inoculation and Dilution* and *Neutralization and Removal of Antimicrobial Activity* under *Preparation of the Sample*. From each level of dilution, three aliquots of 1 g or 1 mL are used to inoculate three

tubes with 9 to 10 mL of *Soybean–Casein Digest Medium*. If necessary, a surface-active agent such as polysorbate 80, or an inactivator of antimicrobial agents, may be added to the medium. Thus, if 3 levels of dilution are prepared, 9 tubes are inoculated.

Incubate all tubes for not more than 3 days between 30° and 35°. If reading of the results is difficult or uncertain owing to the nature of the product to be examined, subculture in the same broth or in *Soybean–Casein Digest Agar Medium* for 1 to 2 days at the same temperature, and use these results. Determine the MPN of microorganisms per g or mL of the product to be examined from *Table 2*.

Table 2. Most-Probable Number Values of Bacteria

Observed Combinations of Numbers of Tubes Showing Growth in Each Set			MPN per g or per mL of Product	95% Confidence Limits
Number of g or mL of Product per Tube				
0.1	0.01	0.001		
3	3	3	more than 1100	—
3	3	2	1100	300–4800
3	3	1	500	200–2400
3	3	0	200	100–1400
3	2	2	210	80–640
3	2	1	150	50–510
3	2	0	90	30–390
3	1	1	70	20–280
3	1	0	40	20–210
3	0	1	40	10–180
3	0	0	23	7–129
2	2	0	21	8–63
2	1	1		
20	8–61			
2	1	0	15	5–50
2	0	1	14	5–48
2	0	0	9	2–38
1	2	0	11	4–35
1	1	0	7	2–28
1	0	0	4	1–21
0	1	0	3	<1–17
0	0	0	<3	—

RESULTS AND INTERPRETATION

When verifying the suitability of the *Membrane Filtration Method* or the *Plate-Count Method*, a count of any of the test organisms differing by not more than a factor of 2 (0.3 log) from the value of the control in the absence of the product must be obtained.

When verifying the suitability of the *MPN Method,* the calculated value from the inoculum must be within 95% confidence limits of the results obtained.

TESTING OF PRODUCTS

Sample Size

Unless otherwise directed, use sample(s) of 10 g or 10 mL of the product to be examined taken with the precautions referred to above. For fluids or solids in aerosol form, sample 10 containers. For transdermal patches, sample 10 patches.

The amount of sample tested may be reduced for active substances that will be formulated under the following conditions: the amount per dosage unit (e.g., tablet, capsule) is less than or equal to 1 mg, or the amount per g or mL (for preparations not presented in dose units) is less than 1 mg. In these cases, the amount of sample tested is not less than the amount present in 10 dosage units or 10 g or 10 mL of the product.

For materials used as bulk active substances where sample quantity is limited or batch size is extremely small (i.e., less than 1000 mL or 1000 g), test 1% of the batch.

For products where the total number of entities in a batch is less than 200 (e.g., samples used in clinical trials), the sample size may be reduced to 2 units, or 1 unit if the size is less than 100.

Select the sample(s) at random from the bulk material or from the available containers of the preparation. To obtain the required quantity, mix the contents of a sufficient number of containers to provide the sample.

Examination of the Product Sample

MEMBRANE FILTRATION

Use a filtration apparatus designed to allow the transfer of the filter to the medium. Prepare the sample using a method that has been shown to be suitable (see *Growth Promotion Test and Suitability of the Counting Method*), transfer the appropriate quantity to each of two membrane filters, and filter immediately. Wash each filter following the procedure shown to be suitable.

For the determination of TAMC, transfer one of the membrane filters to the surface of *Soybean–Casein Digest Agar Medium*. For the determination of TYMC, transfer the other membrane to the surface of *Sabouraud Dextrose Agar Medium*. Incubate the plate of *Soybean–Casein Digest Agar Medium* for 3 to 5 days between 30° and 35° and the plate of *Sabouraud Dextrose Agar Medium* for 5 to 7 days between 20° and 25°. Calculate the number of cfu per g or per mL of product.

When examining transdermal patches, separately filter 10% of the volume of the preparation as directed for *Preparation of the Sample* through each of two sterile filter membranes. Transfer one membrane to *Soybean–Casein Digest Agar Medium* for TAMC and the other membrane to *Sabouraud Dextrose Agar Medium* for TYMC.

PLATE-COUNT METHODS

Pour-Plate Method—Prepare the sample using a method that has been shown to be suitable (see *Growth Promotion Test and Suitability of the Counting Method*). Prepare for each medium at least two Petri dishes for each level of dilution. Incubate the plates of *Soybean–Casein Digest Agar Medium* for 3 to 5 days between 30° and 35° and the plates of *Sabouraud Dextrose Agar Medium* for 5 to 7 days between 20° and 25°. Select the plates corresponding to a given dilution and showing the highest number of colonies less than 250 for TAMC and less than 50 for TYMC. Take the arithmetic mean per culture medium of the counts, and calculate the number of cfu per g or per mL of product.

Surface-Spread Method—Prepare the sample using a method that has been shown to be suitable (see *Growth Promotion Test and Suitability of the Counting Method*). Prepare at least two Petri dishes for each medium and each level of dilution. For incubation and calculation of the number of cfu, proceed as directed for the *Pour-Plate Method.*

MPN METHOD

Prepare and dilute the sample using a method that has been shown to be suitable (see *Growth Promotion Test and Suitability of the Counting Method*). Incubate all tubes for 3 to 5 days between 30° and 35°. Subculture if necessary, using the procedure shown to be suitable. For each level of dilution, record the number of tubes showing microbial growth. Determine the MPN of bacteria per g or mL of the product to be examined from *Table 2*.

Interpretation of Results

The TAMC is considered to be equal to the number of cfu found on *Soybean–Casein Digest Agar Medium*. If colonies of fungi are detected on this medium, they are counted as part of the TAMC. The total combined yeasts and mould count (TYMC) is considered to be equal to the number of cfu found on *Sabouraud Dextrose Agar Medium.* If colonies of bacteria are detected on this medium, they are counted as part of the TYMC. If the count is carried out by the *MPN Method*, the calculated value is the TAMC.

When a criterion for microbiological quality is prescribed, it is interpreted as follows:

- 10^1 cfu: maximum acceptable count is 20;
- 10^2 cfu: maximum acceptable count is 200;
- 10^3 cfu: maximum acceptable count is 2000; and so forth.

BRIEFING

⟨62⟩ Microbiological Examination of Nonsterile Products: Tests for Specified Microorganisms. This proposed new chapter, which previously appeared as a Pharmacopeial Discussion Group (PDG) Stage 4 OFFICIAL INQUIRY (see 2313 of *PF* 27(2) [Mar.–Apr. 2001]), has undergone extensive changes, and therefore the previous Stage 4 document is hereby cancelled and replaced by this new PDG **Stage 4 OFFICIAL INQUIRY**. The following changes were based upon comments received in response to the previous Stage 4 document and upon discussion held by experts from the EP, JP, and USP:

(1) Incubation temperature for *Escherichia coli* has been raised to between 42° and 44°. This provides better selectivity.
(2) Sample size was decreased to 1 g.
(3) Regarding selective agars for the detection of *Salmonella* species, *Pseudomonas aeruginosa,* and *Staphylococcus aureus,* only one medium was retained in each case.
(4) The method for growing *Candida albicans* has been replaced by the method used for the determination of TCYM.
(5) Specific instructions for the sterilization of media have been removed.

Other changes of lesser significance have been made throughout the text. Comments regarding this Stage 4 proposal are invited and should be submitted by **31 October 2003**.

(AMB: D.A. Porter) RTS—40089-1

Add the following:

⟨62⟩ MICROBIOLOGICAL EXAMINATION OF NONSTERILE PRODUCTS: TESTS FOR SPECIFIED MICROORGANISMS

INTRODUCTION

The tests described hereafter will allow determination of the absence of or limited occurrence of specified microorganisms that may be detected under the conditions described.

The tests are designed primarily to determine whether a substance or preparation complies with an established specification for microbiological quality. When used for such purposes, follow the instructions given below, including the number of samples taken, and interpret the results as directed below.

Alternative microbiological procedures, including automated methods, may be used, provided that their equivalence to the Pharmacopeial method has been demonstrated.

GENERAL PROCEDURES

The preparation of samples is carried out as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩.

If the product to be examined has antimicrobial activity, this is, insofar as possible, removed or neutralized (see *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩).

If surface-active substances are used for sample preparation, their absence of toxicity for microorganisms and their compatibility with any inactivators used must be demonstrated as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩.

NUTRITIVE AND SELECTIVE PROPERTIES OF THE MEDIA AND SUITABILITY OF THE TEST

The ability of the test to detect microorganisms in the presence of product must be established. Suitability must be confirmed if a change in testing performance or in the product, which may affect the outcome of the test, is introduced.

Preparation of Test Strains

Use standardized stable suspensions or prepare as stated below. Seed lot culture maintenance techniques (seed-lot systems) are used so that the viable microorganisms used for inoculation are not more than five passages removed from the original master seed-lot.

AEROBIC MICROORGANISMS

Grow the bacterial test strains separately in containers containing *Soybean–Casein Digest Medium* or *Soybean–Casein Digest Agar Medium* between 30° and 35° for 18 to 24 hours. Grow the test strain for *Candida albicans* separately on *Sabouraud Dextrose Agar Medium* or *Sabouraud Dextrose Medium* between 20° and 25° for 2 to 3 days.

Staphylococcus aureus	such as ATCC 6538, NCIMB 9518, CIP 4.83, or NBRC 13276
Pseudomonas aeruginosa	such as ATCC 9027, NCIMB 8626, CIP 82.118, or NBRC 13275
Escherichia coli	such as ATCC 8739, NCIMB 8545, CIP 53.126, or NBRC 3972
Salmonella enterica ssp. typhimurium	such as ATCC 14028
or as an alternative *Salmonella enterica ssp. abony*	such as NCTC 6017 or CIP 80.39
Candida albicans	such as ATCC 10231, NCPF 3179, IP 48.72, or NBRC 1594

CLOSTRIDIA

Use *Clostridium sporogenes* such as ATCC 11437 or ATCC 19404 (NCTC 532 or CIP 79.03). Grow the clostridial test strain under anaerobic conditions in *Reinforced Medium for Clostridia* between 30° and 35° for 24 to 48 hours. As an alternative to preparing and then diluting down a fresh suspension of vegetative cells of *C. sporogenes* when verifying the suitability of the test method, a stable spore suspension can be used for test inoculation. The stable spore suspension is maintained between 2° and 8° for a validated period.

Negative Control

To verify the absence of contamination in media a portion of each batch is incubated. To verify testing conditions a negative control is performed using the chosen diluent as the test preparation for each batch of diluent. There must be no growth of microorganisms.

Growth Promotion of the Media

Test each batch of ready-prepared medium and each batch of medium prepared either from dehydrated medium or from ingredients (see *Buffer Solutions and Culture Media*). In appropriate cases, periodic testing of different batches prepared from the same lot of dehydrated medium is acceptable. Verify suitable properties of relevant media as described in *Table 1*.

Table 1. Nutritive, Selective, and Indicative Properties of Media

Medium	Property	Test Strains
Test for bile-tolerant Gram-negative bacteria		
Mossel Enterobacteriaceae Enrichment Broth	Nutritive	*E. coli*
		P. aeruginosa
	Selective	*S. aureus*
Violet Red Bile Glucose Agar Medium	Nutritive + Indicative	*E. coli*
		P. aeruginosa
Test for Escherichia coli		
MacConkey Medium	Nutritive	*E. coli*
	Selective	*S. aureus*
MacConkey Agar Medium	Nutritive + Indicative	*E. coli*
Test for Salmonella		
Rappaport Vassiliadis Salmonella Enrichment Broth	Nutritive	*Salmonella enterica ssp. typhimurium* or *Salmonella enterica ssp. abony*
	Selective	*S. aureus*
Xylose, Lysine, Deoxycholate, Agar Medium	Nutritive + Indicative	*Salmonella enterica ssp. typhimurium* or *Salmonella enterica ssp. abony* *E. coli*

Table 1. Nutritive, Selective, and Indicative Properties of Media (*continued*)

Medium	Property	Test Strains
Test for Pseudomonas aeruginosa		
Cetrimide Agar Medium	Nutritive	*P. aeruginosa*
	Selective	*E. coli*
Test for Staphylococcus aureus		
Mannitol Salt Agar Medium	Nutritive	*S. aureus*
	Selective	*E. coli*
Test for Clostridia		
Reinforced Medium for Clostridia	Nutritive	*C. sporogenes*
Columbia Agar Medium	Nutritive	*C. sporogenes*
Test for Candida albicans		
Sabouraud Dextrose Medium	Nutritive	*C. albicans*
Sabouraud Dextrose Agar Medium	Nutritive + Indicative	*C. albicans*

TEST FOR NUTRITIVE PROPERTIES

Liquid Media—Inoculate a portion of the appropriate medium with a small number (not more than 100 cfu) of the appropriate microorganism. Incubate at the specified temperature for not more than the shortest period of time specified in the test. Clearly visible growth of the microorganism comparable to a previously used batch of medium occurs.

Solid Media—Perform *Surface-Spread Method* (see *Pour-Plate Methods* under *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩), inoculating each plate with a small number (not more than 100 cfu) of the appropriate microorganism. Incubate at the specified temperature for not more than the shortest period of time specified in the test. Colonies are comparable in number and size to a previously used batch of medium.

TEST FOR SELECTIVE PROPERTIES FOR LIQUID OR SOLID MEDIA

Inoculate the appropriate medium with at least 100 cfu of the appropriate microorganism. Incubate at the specified temperature for not less than the longest period of time specified in the test. No growth of the test microorganism occurs.

TEST FOR INDICATIVE PROPERTIES

Perform *Surface-Spread Method* (see *Pour-Plate Methods* under *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩), inoculating each plate with a small number (not more than 100 cfu) of the appropriate microorganism. Incubate at the specified temperature for a period of time within the range specified in the test. Colonies are comparable in appearance and indication reactions to a previously used batch of medium.

Suitability of the Test Method

For each new product to be tested perform sample preparation as directed under *Testing of Products*. Add test strains at the time of homogenization in *Soybean–Casein Digest Medium*. Inoculate the test strains individually. Use a number of microorganisms equivalent to not more than 100 cfu in the final test preparation. Perform the test as directed under *Testing of Products*.

Table 2. Suitability of the Test Method for Each Product

Test Microorganism	Required Outcome
Test for bile-tolerant Gram-negative bacteria:	
E. coli	Growth as described
S. aureus	No growth
Test for Escherichia coli:	
E. coli	Growth as described
S. aureus	No growth
Test for Salmonella:	
Salmonella enterica ssp. typhimurium or *Salmonella enterica ssp. abony*	Growth as described
S. aureus	No growth
Test for Pseudomonas aeruginosa:	
P. aeruginosa	Growth as described
E. coli	No growth
Test for Staphylococcus aureus:	
S. aureus	Growth as described
E. coli	No growth

Any antimicrobial activity of the product necessitates a modification of the test procedure (see *Neutralization and Removal of Antimicrobial Activity* under *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩).

TESTING OF PRODUCTS

Bile-Tolerant Gram-Negative Bacteria

SAMPLE PREPARATION AND PRE-INCUBATION

Prepare a sample using a 1 in 10 dilution of not less than 1 g of the product to be examined as described under *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, but using *Soybean–Casein Digest Medium* as the chosen diluent. Homogenize, and incubate between 20° and 25° for a time sufficient to resuscitate the bacteria but not sufficient to encourage multiplication of the organisms (usually 2 hours but not more than 5 hours).

TEST FOR ABSENCE

Use the volume corresponding to the limit required (see *Sample Preparation and Pre-Incubation*) to inoculate a suitable amount (as determined under *Suitability of the Test Method*), of *Mossel Enterobacteriaceae Enrichment Broth*. When testing transdermal patches, filter the volume of sample corresponding to one patch (see *Transdermal Patches* under *Preparation of the Sample* in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩) through a sterile filter membrane, and place in 100 mL of *Mossel Enterobacteriaceae Enrichment Broth*. Incubate between 30° and 35° for 24 to 48 hours. Subculture on plates of *Violet Red Bile Glucose Agar Medium*. Incubate between 30° and 35° for 18 to 24 hours. The product complies with the test if there is no growth of red colonies surrounded by a reddish precipitate.

QUANTITATIVE TEST

Selection and Subculture—Inoculate suitable quantities of *Mossel Enterobacteriaceae Enrichment Broth* with the preparation as directed under *Sample Preparation and Pre-Incubation* and/or dilutions of it containing respectively

0.1 g, 0.01 g, and 0.001 g (or 0.1 mL, 0.01 mL, and 0.001 mL) of the product to be examined. Incubate between 30° and 35° for 24 to 48 hours. Subculture each of the cultures on a plate of *Violet Red Bile Glucose Agar Medium*. Incubate between 30° and 35° for 18 to 24 hours.

Interpretation—Growth of red colonies, surrounded by a reddish precipitate, constitutes a positive result. Note the smallest quantity of the product that gives a positive result and the largest quantity that gives a negative result. Determine from *Table 3* the probable number of bacteria.

Table 3.

Results for Each Quantity of Product			Probable Number of Bacteria per g of Product
0.1 g or 0.1 mL	0.01 g or 0.01 mL	0.001 g or 0.001 mL	
+	+	+	more than 10^3
+	+	–	less than 10^3 and more than 10^2
+	–	–	less than 10^2 and more than 10
–	–	–	less than 10

Escherichia coli

SAMPLE PREPARATION AND PRE-INCUBATION

Prepare a sample using a 1 in 10 dilution of not less than 1 g of the product to be examined as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩ and use 10 mL, or the quantity corresponding to 1 g or 1 mL, to inoculate a suitable amount (as determined under *Suitability of the Test Method*) of *Soybean–Casein Digest Medium*. Homogenize, and incubate between 30° and 35° for 18 to 24 hours.

SELECTION AND SUBCULTURE

Shake the container, transfer 1 mL of *Soybean–Casein Digest Medium* to 100 mL of *MacConkey Medium*, and incubate between 42° and 44° for 24 to 48 hours. Subculture on a plate of *MacConkey Agar Medium* between 30° and 35° for 18 to 72 hours.

INTERPRETATION

Growth of colonies indicates the possible presence of *E. coli*. This is confirmed by suitable identification tests. The product complies with the test if no colonies are present or if the identification tests are negative.

Salmonella

SAMPLE PREPARATION AND PRE-INCUBATION

Prepare the product to be examined as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, and use the quantity corresponding to 1 g or 1 mL to inoculate a suitable amount (as determined under *Suitability of the Test Method*) of *Soybean–Casein Digest Medium*. Homogenize, and incubate between 30° and 35° for 18 to 24 hours.

SELECTION AND SUBCULTURE

Transfer 1 mL of *Soybean–Casein Digest Medium* to 10 mL of R*appaport Vassiliadis Salmonella Enrichment Broth*, and incubate between 30° and 35° for 18 to 24 hours. Subculture on plates of *Xylose, Lysine, Deoxycholate Agar Medium*. Incubate between 30° and 35° for 18 to 48 hours.

INTERPRETATION

The possible presence of *Salmonella* is indicated by the growth of well-developed, red colonies, with or without black centers. This is confirmed by suitable identification tests. The product complies with the test if colonies of the types described are not present or if the confirmatory identification tests are negative.

Pseudomonas aeruginosa

SAMPLE PREPARATION AND PRE-INCUBATION

Prepare a sample using a 1 in 10 dilution of not less than 1 g of the product to be examined as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, and use 10 mL or the quantity corresponding to 1 g or 1 mL to inoculate a suitable amount (as determined under *Suitability of the Test Method*) of *Soybean–Casein Digest Medium*, and homogenize. When testing transdermal patches, filter the volume of sample corresponding to one patch of the preparation (see *Transdermal Patches* under *Preparation of the Sample* in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩) through a sterile filter membrane, and place in 100 mL of *Soybean–Casein Digest Medium*. Incubate between 30° and 35° for 18 to 24 hours.

SELECTION AND SUBCULTURE

Subculture on a plate of *Cetrimide Agar Medium*, and incubate between 30° and 35° for 18 to 72 hours.

INTERPRETATION

Growth of colonies indicates the possible presence of *P. aeruginosa*. This is confirmed by suitable identification tests. The product complies with the test if colonies are not present or if the confirmatory identification tests are negative.

Staphylococcus aureus

SAMPLE PREPARATION AND PRE-INCUBATION

Prepare a sample using a 1 in 10 dilution of not less than 1 g of the product to be examined as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, and use 10 mL or the quantity corresponding to 1 g or 1 mL to inoculate a suitable amount (as determined under *Suitability of the Test Method*) of *Soybean–Casein Digest Medium*, and homogenize. When testing transdermal patches, filter the volume of sample corresponding to one patch of the preparation (see *Transdermal Patches* under *Preparation of the Sample* in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩) through a sterile filter membrane, and place in 100 mL of *Soybean–Casein Digest Medium*. Incubate between 30° and 35° for 18 to 24 hours.

SELECTION AND SUBCULTURE

Subculture on a plate of *Mannitol Salt Agar Medium*, and incubate between 30° and 35° for 18 to 72 hours.

INTERPRETATION

The possible presence of *S. aureus* is indicated by the growth of yellow or white colonies surrounded by a yellow zone. This is confirmed by suitable identification tests. The product complies with the test if colonies of the types described are not present or if the confirmatory identification tests are negative.

Clostridia

SAMPLE PREPARATION AND HEAT TREATMENT

Prepare the product to be examined as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩. Take two equal portions corresponding to 1 g or 1 mL of the product to be examined. Heat one portion at 80° for 10 minutes, and cool rapidly. Do not heat the other portion.

SELECTION AND SUBCULTURE

Transfer 10 mL of each of the homogenized portions to two containers (38 × 200 mm), or other suitable containers, containing 100 mL of *Reinforced Medium for Clostridia*. Incubate under anaerobic conditions between 30° and 35° for 48 hours. After incubation, make subcultures from each tube on *Columbia Agar Medium*, and incubate under anaerobic conditions between 30° and 35° for 48 hours.

INTERPRETATION

The occurrence of anaerobic growth of rods (with or without endospores) giving a negative catalase reaction indicates the presence of *Clostridia*. If no anaerobic growth of microorganisms is detected on *Columbia Agar Medium* or the catalase test is positive, the product complies with the test.

Candida albicans

SAMPLE PREPARATION AND PRE-INCUBATION

Prepare the product to be examined as described in *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩, and use 10 mL, or the quantity corresponding to 1 g or 1 mL, to inoculate 100 mL of *Sabouraud Dextrose Medium*, and homogenize. Incubate between 20° and 25° for 5 to 7 days.

SELECTION AND SUBCULTURE

Subculture on a plate of *Sabouraud Dextrose Agar Medium*, and incubate between 20° and 25° for 2 days.

INTERPRETATION

Growth of white colonies may indicate the presence of *C. albicans*. This is confirmed by suitable identification tests. The product complies with the test if spores are not present or if the confirmatory identification tests are negative.

BUFFER SOLUTIONS AND CULTURE MEDIA

The following solutions and culture media have been found satisfactory for the purposes for which they are prescribed in the test for microbial contamination in the Pharmacopeia.

pH 7.2 Phosphate Buffer

Stock Buffer Solution—Transfer 34 g of potassium hydrogen phosphate to a 1000-mL volumetric flask, dissolve in 500 mL of *Purified Water*, adjust with about 175 mL of sodium hydroxide to a pH of 7.2 ± 0.2, add *Purified Water* to volume, and mix. Dispense in containers, and sterilize. Store at a temperature between 2° to 8°.

Prepare a mixture of *Purified Water* and *Stock Buffer Solution* (800:1), and sterilize.

pH 7.0 Buffered Sodium Chloride-Peptone Solution

Monobasic Potassium Phosphate	3.6 g
Dibasic Sodium Phosphate, Dihydrate (equivalent to 0.067 M phosphate)	7.2 g
Sodium Chloride	4.3 g
Peptone (meat or casein)	1.0 g
Purified Water	1000 mL

Sterilize in an autoclave using a validated cycle.

Soybean–Casein Digest Medium

Pancreatic Digest of Casein	17.0 g
Papaic Digest of Soybean Meal	3.0 g
Sodium Chloride	5.0 g
Dibasic Potassium Phosphate	2.5 g
Dextrose ($C_6H_{12}O_6 .H_2O$)/($C_6H_{12}O_6$)	2.5/2.3 g
Purified Water	1000 mL

Adjust the pH so that after sterilization it is 7.3 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

Soybean–Casein Digest Agar Medium

Pancreatic Digest of Casein	15.0 g
Papaic Digest of Soybean Meal	5.0 g
Sodium Chloride	5.0 g
Agar	15.0 g
Purified Water	1000 mL

Adjust the pH so that after sterilization it is 7.3 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

Sabouraud Dextrose Agar Medium

Dextrose	40.0 g
Mixture of Peptic Digest of Animal Tissue and Pancreatic Digest of Casein (1:1)	10.0 g
Agar	15.0 g
Purified Water	1000 mL

Adjust the pH so that after sterilization it is 5.6 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

Potato Dextrose Agar Medium

Infusion from potatoes	200 g
Dextrose	20.0 g
Agar	15.0 g
Purified Water	1000 mL

Adjust the pH so that after sterilization it is 5.6 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

Sabouraud Dextrose Medium

Dextrose	20.0 g
Mixture of Peptic Digest of Animal Tissue and Pancreatic Digest of Casein (1:1)	10.0 g
Purified Water	1000 mL

Adjust the pH so that after sterilization it is 5.6 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

Mossel Enterobacteriaceae Enrichment Broth	
Pancreatic Digest of Gelatin	10.0 g
Glucose Monohydrate	5.0 g
Dehydrated Ox Bile	20.0 g
Monobasic Potassium Phosphate	3.0 g
Dibasic Sodium Phosphate, Dihydrate	8.0 g
Brilliant Green	15 mg
Purified Water	1000 mL

Adjust the pH so that after heating it is 7.2 ± 0.2 at 25°. Heat at 100° for 30 minutes, and cool immediately.

Violet Red Bile Glucose Agar Medium	
Yeast Extract	3.0 g
Pancreatic Digest of Gelatin	7.0 g
Bile Salts	1.5 g
Sodium Chloride	5.0 g
Glucose Monohydrate	10.0 g
Agar	15.0 g
Neutral Red	30 mg
Crystal Violet	2 mg
Purified Water	1000 mL

Adjust the pH so that after heating it is 7.4 ± 0.2 at 25°. Heat to boiling; do not heat in an autoclave.

MacConkey Medium	
Pancreatic Digest of Gelatin	20.0 g
Lactose Monohydrate	10.0 g
Dehydrated Ox Bile	5.0 g
Bromocresol Purple	10 g
Purified Water	1000 mL

Adjust the pH so that after sterilzation it is 7.3 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

MacConkey Agar Medium	
Pancreatic Digest of Gelatin	17.0 g
Peptones (meat and casein)	3.0 g
Lactose Monohydrate	10.0 g
Sodium Chloride	5.0 g
Bile Salts	1.5 g
Agar	13.5 g
Neutral Red	30.0 mg
Crystal Violet	1 mg
Purified Water	1000 mL

Adjust the pH so that after sterilization it is 7.1 ± 0.2 at 25°. Boil for 1 minute with constant shaking, then sterilize in an autoclave using a validated cycle.

Rappaport Vassiliadis Salmonella Enrichment Broth	
Soya Peptone	4.5 g
Magnesium Chloride Hexahydrate	29.0 g
Sodium Chloride	8.0 g
Dipotassium Phosphate	0.4 g
Potassium Dihydrogen Phosphate	0.6 g
Malachite Green	0.036 g
Purified Water	1000 mL

Dissolve, warming slightly. Sterilize in an autoclave using a validated cycle, at a temperature not exceeding 115°. The pH is to be 5.2 ± 0.2 at 25° after heating and autoclaving.

Xylose, Lysine, Deoxycholate Agar Medium	
Xylose	3.5 g
L-Lysine	5.0 g
Lactose Monohydrate	7.5 g
Sucrose	7.5 g
Sodium Chloride	5.0 g
Yeast Extract	3.0 g
Phenol Red	80 mg
Agar	13.5 g
Sodium Deoxycholate	2.5 g
Sodium Thiosulphate	6.8 g
Ferric Ammonium Citrate	0.8 g
Purified Water	1000 mL

Adjust the pH so that after heating it is 7.4 ± 0.2 at 25°. Heat to boiling, cool to 50°, and pour into Petri dishes. Do not heat in an autoclave.

Cetrimide Agar Medium	
Pancreatic Digest of Gelatin	20.0 g
Magnesium Chloride	1.4 g
Dipotassium Sulphate	10.0 g
Cetrimide	0.3 g
Agar	13.6 g
Purified Water	1000 mL
Glycerol	10.0 mL

Heat to boiling for 1 minute with shaking. Adjust the pH so that after sterilization it is 7.2 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

Mannitol Salt Agar	
Pancreatic Digest of Casein	5.0 g
Peptic Digest of Animal Tissue	5.0 g
Beef Extract	1.0 g
D-Mannitol	10.0 g
Sodium Chloride	75.0 g
Agar	15.0 g
Phenol Red	0.025 g
Purified Water	1000 mL

Heat to boiling for 1 minute with shaking. Adjust the pH so that after sterilization it is 7.4 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle.

Reinforced Medium for Clostridia	
Beef Extract	10.0 g
Peptone	10.0 g
Yeast Extract	3.0 g
Soluble Starch	1.0 g
Glucose Monohydrate	5.0 g
Cysteine Hydrochloride	0.5 g
Sodium Chloride	5.0 g
Sodium Acetate	3.0 g
Agar	0.5 g
Purified Water	1000 mL

Hydrate the agar, and dissolve by heating to boiling with continuous stirring. If necessary, adjust the pH so that after sterilization it is about 6.8 at 25°. Sterilize in an autoclave using a validated cycle.

Columbia Agar Medium	
Pancreatic Digest of Casein	10.0 g
Meat Peptic Digest	5.0 g
Heart Pancreatic Digest	3.0 g
Yeast Extract	5.0 g
Maize Starch	1.0 g
Sodium Chloride	5.0 g
Agar, according to gelling power	10.0–15.0 g
Purified Water	1000 mL

Hydrate the agar, and dissolve by heating to boiling with continuous stirring. If necessary, adjust the pH so that after sterilization it is 7.3 ± 0.2 at 25°. Sterilize in an autoclave using a validated cycle. Allow to cool to between 45° and 50°; add, if necessary, gentamicin sulfate corresponding to 20 mg of gentamicin base and pour into Petri dishes.

GENERAL CHAPTERS

General Information

BRIEFING

⟨1111⟩ Microbiological Quality of Nonsterile Pharmaceutical Products, *USP 26* page 2380 and page 916 of *PF* 28(3) [May–June 2002]. This proposed revision, which previously appeared as a Pharmacopeial Discussion Group (PDG) PROPOSAL STAGE 3 document, is now forwarded to PDG as **OFFICIAL INQUIRY Stage 4**. The following changes were based on comments received in response to the Stage 3 document and discussions held by experts from the EP, JP, and USP:

1. The term "objectionable" has been deleted.
2. The decision tree (*Figure 1*) for selection of objectionable microorganisms present on selective media has been deleted, because it has caused confusion and the guidance it provided did not prove to be useful.
3. The term "Microbial Enumeration Targets" has been replaced by the term "Criteria for Microbiological Quality".
4. Criteria for total combined yeasts and molds count (TCYM) have been added for preparations for oromucosal, gingival, cutaneous, nasal, auricular, vaginal, and inhalation uses, and for transdermal patches.
5. Preparations for oral use have been split into two categories (liquid and solid), because different acceptance criteria are applied in view of the different potential for contamination.
6. Herbal drugs have been excluded from the scope of International Harmonization, because they are dealt with differently from region to region.
7. Nonsterile substances for pharmaceutical use have been included into the scope of International Harmonization, to give general guidance on microbiological quality; specific monographs will continue to give mandatory requirements where appropriate.

Other changes of lesser significance have been made throughout the text.

Deadline for comments: **31 October 2003**.

(AMB: D. Porter) RTS—40090-1

Change to read:

■⟨1111⟩ MICROBIOLOGICAL QUALITY OF NONSTERILE PHARMACEUTICAL PRODUCTS

The presence of certain specific microorganisms in nonsterile preparations may have the potential to reduce or even inactivate the therapeutic activity of the product and has a potential to adversely affect the health of the patient. Manufacturers therefore, have to ensure a low bioburden of finished dosage forms by implementing current guidelines on Good Manufacturing Practice during the manufacture, storage, and distribution of pharmaceutical preparations.

Microbial examination of nonsterile products is performed according to the methods given in the texts on *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* ⟨61⟩ and *Microbiological Examination of Nonsterile Products: Tests for Specified Microorganism* ⟨62⟩. Acceptable criteria for nonsterile dosage forms based upon the total aerobic microbial count (TAMC)

and the total combined yeasts and molds count (TYMC) are given in *Tables 1* and *2*. Criteria are based on individual results or on the average of replicate counts when replicate counts are performed (e.g., direct plating methods). *Table 1* includes a listing of specified microorganisms for which criteria are set.

Table 1. Criteria for Microbiological Quality Nonsterile Dosage Forms

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)	Specified Microorganism(s)
Solid preparations for oral use*	10^3	10^2	Absence of *Escherichia coli* (1 g or 1 mL)
Liquid preparations for oral use*	10^2	10^1	Absence of *Escherichia coli* (1 g or 1 mL)
Rectal use	10^3	10^2	—
Oromucosal use Gingival use Cutaneous use Nasal use Auricular use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonasaeruginosa* (1 g or 1 mL)
Vaginal use	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Escherichia coli* (1 g or 1 mL) Absence of *Candida albicans* (1 g or 1 mL)
Transdermal patches (limits for one patch including adhesive layer and backing)	10^2	10^1	Absence of *Staphylococcus aureus* (1 patch) Absence of *Pseudomonas aeruginosa* (1 patch)

Table 1. Criteria for Microbiological Quality Nonsterile Dosage Forms (*continued*)

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)	Specified Microorganism(s)
Inhalation use (except for nebulizer solutions, which must be sterile)	10^2	10^1	Absence of *Staphylococcus aureus* (1 g or 1 mL) Absence of *Pseudomonas aeruginosa* (1 g or 1 mL) Absence of bile-tolerant Gram-negative bacteria (1 g or 1 mL)

* For oral dosage forms, other than those covered by *Table 2*, containing raw materials of natural (animal, vegetable, or mineral) origin for which antimicrobial pretreatment is not feasible and for which the competent authority accepts microbial contamination of the raw material exceeding 10^3 viable microorganisms per g or per mL, the enumeration targets are the following: TAMC, 10^4 cfu per g or per mL; TYMC, 10^2 cfu per g or per mL. Tests for specified microorganisms show not more than 10^2 enterobacteria and certain other Gram-negative bacteria per g or per mL, absence of *Salmonella* (10 g or 10 mL), absence of *E. coli* (1 g or 1 mL) and absence of *Staphylococcus aureus* (1 g or 1 mL).

Table 2. Criteria for Microbiological Quality of Nonsterile Substances for Pharmaceutical Use

Route of Administration	Total Aerobic Microbial Count (cfu/g or cfu/mL)	Total Combined Yeasts/Molds Count (cfu/g or cfu/mL)
Substances for pharmaceutical use	10^3	10^2

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

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

BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How To Use PF*), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:

(PA5: K. Russo) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

STIMULI TO THE REVISION PROCESS

This section may contain the following:

- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

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Instructions to Authors

Contributions in the form of original research reports, evaluations of new and existing compendial methods, and other commentaries and articles relevant to drug standards or to *USP–NF* revision will be considered for publication in the *Pharmacopeial Forum* under the section *Stimuli to the Revision Process*. Manuscripts are received with the explicit understanding that they have not been published previously and that they are not simultaneously under consideration by any other publication.

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Abstract—Include an abstract of not more than 250 words stating the purpose and the results or conclusions of the article.

References—Consult a current copy of the *Pharmacopeial Forum* and the *ACS Style Guide* for assistance with reference style.

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Pharmacopeial Forum
Executive Secretariat, USP
12601 Twinbrook Pkwy.
Rockville, MD 20852

Development of a Compendial Taxonomy and Glossary for Pharmaceutical Dosage Forms

Keith Marshall, *Chair, USP Pharmaceutical Dosage Forms Expert Committee*; Thomas S. Foster, *Chair, USP Biopharmaceutics Expert Committee*; Herbert S. Carlin, *Chair, USP Nomenclature and Labeling Expert Committee*; and Roger L. Williams, *EVP & CEO, United States Pharmacopeia*

ABSTRACT Members of the Pharmaceutical Dosage Forms Expert Committee (PDF EC) began development of this pharmaceutical dosage form taxonomy scheme and related glossary more than a year ago. In November 2002, an Ad Hoc Committee composed of members with expertise in pharmaceutical dosage forms, biopharmaceutics, and nomenclature was formed to work with the PDF EC in this endeavor.

The Stimuli article presented here represents the combined effort of this Ad Hoc Committee and the PDF EC. Portions of the PDF EC–approved taxonomy charts and glossary were subsequently revised by members of the Ad Hoc Committee for clarity and to address nomenclature issues. This article is the first step in the public review and comment process. Further modifications to the taxonomy scheme and glossary are anticipated.

Readers are invited and encouraged to submit comments and suggestions regarding the completeness, clarity, and utility of this taxonomy scheme and glossary. Receipt of such comments will facilitate revision of the taxonomy chart and glossary and their advancement in the revision review/adoption process.

INTRODUCTION

As part of its assignment to revise General Chapter <1151> *Pharmaceutical Dosage Forms*, the Pharmaceutical Dosage Forms Expert Committee (PDF EC) undertook during 2002 the development of a taxonomic scheme for the categorization of pharmaceutical dosage forms. The intent is that this scheme will clarify the content of *USP–NF* and make it more user-friendly. The taxonomy and its associated glossary provide the following benefits to users of the compendia:

- a uniform way of categorizing pharmaceutical dosage forms;
- a tool for finding information and linking specific dosage form monographs and general chapters;
- a rational linkage between dosage forms and their compendial specifications; and
- a linkage between dosage form drug substance(s) and therapeutic use.

In particular, if individual dosage forms can be more easily linked with their specifications or performance tests, both the manufacturer and the regulator will have a much clearer knowledge of the specifications generally needed to demonstrate compliance. Development of this taxonomy is also seen by USP as a mechanism for linking the endeavors of other USP Expert Committees, the Food and Drug Administration (FDA), Health Level 7 (HL7) (*1*), and the International Conference on Harmonization (ICH) in this field. It has been reported that FDA has a goal to standardize the established names of dosage forms to facilitate electronic transactions within the Agency.

In an effort to standardize names, FDA is also looking at nomenclature use in other countries. FDA and the USP Expert Committee on Nomenclature and Labeling work together on USP nomenclature for new products for which there are no USP dosage form descriptors. Many of the FDA and USP terms match or are close—but many of them do not match. The CDER Data Standards Manual has many dosage forms that USP does not have.

TAXONOMY

The currently suggested taxonomy chart was developed by the PDF EC with assistance from members of the Biopharmaceutics Expert Committee and the Nomenclature and Labeling Expert Committee. This chart is based on the *tier* concept, with the first tier delineating dosage forms according to the route of administration by which the drug substance is delivered.

The second tier is based on the general type of dosage form involved and its physical properties, i.e., solid, semisolid, liquid, gas, or aerosol. Each one of these groupings contains its own subsections listing the specific presentation of the dosage form, e.g., tablet, cream, insert, etc. This second tier facilitates downward expansion into the third tier, which is based on the type of release pattern of the drug substance and performance characteristics of the dosage form.

With such a scheme, any dosage form for any drug substance can be unambiguously identified by a combination of taxonomic terms from each tier, taking the form:

[drug substance] [route of administration] [physical state] [release pattern].

GLOSSARY

The glossary contains an introductory statement indicating that the definitions are for information only and for use in understanding the pharmaceutical dosage forms taxonomy. In the interest of the ongoing harmonization efforts,

the terms used in the taxonomy and glossary generally correspond with those definitions used by FDA, EP, and JP. Dosage form listings in the glossary follow the convention used in USP monograph titles.

The glossary has two parts. Except where indicated, the first part includes definitions associated with those dosage forms that appear in USP monograph titles, i.e., that appear in the taxonomy scheme, plus certain terms that have been agreed upon by USP and FDA but are not yet used in USP monograph titles.

The second part of the glossary includes definitions of some nonpreferred and/or outdated terms that are included only for completeness and electronic searching but with a notation directing the user to the preferred terms in Part 1. It also includes definitions of other terms that are not acceptable for use in *USP–NF* but are deemed to be helpful to the reader because they provide information about dosage form terminology used in other regions.

The general information chapter ⟨1151⟩ *Pharmaceutical Dosage Forms* will not contain subheadings for, or disquisitions on, the dosage form terms contained in Part 2 of the glossary.

CONCLUSION

In developing this taxonomy and glossary, every effort was made to keep them as simple as possible and to avoid duplication. This is viewed by USP as a positive move that may make *USP–NF* more user-friendly. Specifically, it will facilitate electronic searches in a manner that is not currently possible.

It should also be obvious that the taxonomic convention will facilitate the identification of clear associations between related groups of dosage forms and logical standards that should be uniformly applied. Consequently, in accordance with the tests and general chapters (or lack thereof), USP Expert Committees could be assigned or Advisory Panels could be formed to develop and revise the needed tests and general chapters, e.g., an Advisory Panel on Topicals or one on Performance Tests.

In the future it likely will be necessary to expand the number of categories in this taxonomy and glossary to accommodate entirely new types of dosage forms as required by the novel sources of drug substances now beginning to emerge. Likewise, there is Expert Committee agreement that this taxonomy should not limit new naming conventions. It is vital that new dosage form names be published in *USP–NF* to publicly announce the establishment of new dosage forms because FDA uses *USP–NF* as an information source for dosage-form nomenclature. There are also global implications associated with this nomenclature process, e.g., harmonization via ICH and HL7.

PUBLIC COMMENTS ABOUT THE TAXONOMY

Reader comments regarding the suggested taxonomy and glossary are invited. These comments should be submitted to Dr. W. Larry Paul at USP Headquarters, 12601 Twinbrook Parkway, Rockville, MD 20852-1790, by 28 November 2003.

REFERENCE

1. Founded in 1987, Health Level Seven, Inc. (http://www.HL7.org) is a not-for-profit, ANSI-accredited standards developing organization whose mission is to provide a comprehensive framework and related standards for the exchange, integration, sharing, and retrieval of electronic health information that supports clinical practice and the management, delivery, and evaluation of health services. Its 2200 members represent more than 500 corporate members, including 90 percent of the largest information systems vendors serving health care. HL7 has the specific goal to create flexible, cost-effective standards, guidelines, and methodologies to enable health care information system interoperability and sharing of electronic health records. The HL7 data interchange standards have been recommended by the National Committee on Vital and Health Statistics (NCVHS) for national adoption within the United States.

   HL7 has created ANSI standards for the transmission of drug orders, drug dispensing, and patient drug administration transactions. In this context, it is essential that the codes used for drugs be accurate, readily available, easy to use, and stable. Drug codes that meet these qualifications can be used for detecting drug–drug interactions, dosing errors, and drug allergies, as well as efficient reporting of adverse drug events. By means of these capabilities, accurate drug codes ultimately lead to decreased costs and improved patient safety.

USP Expert Committee on Pharmaceutical Dosage Forms

Categories of Pharmaceutical Dosage Forms
A Taxonomic Proposal

The taxonomic charts given here incorporate only dosage forms that are actually named in USP–NF monographs.

FIRST TIER

Delineated by the region of the body to which the drug substance is first delivered by the dosage form.

SECOND TIER

The criterion for this grouping is based on the general type of dosage form involved.

THIRD TIER

Individual dosage forms grouped depending on the release pattern of the drug substance.

NOTE: For some dosage forms it may be advisable to preface titles with a descriptor, e.g., "topical cream," "vaginal insert," or "otic solution."

Figure 1

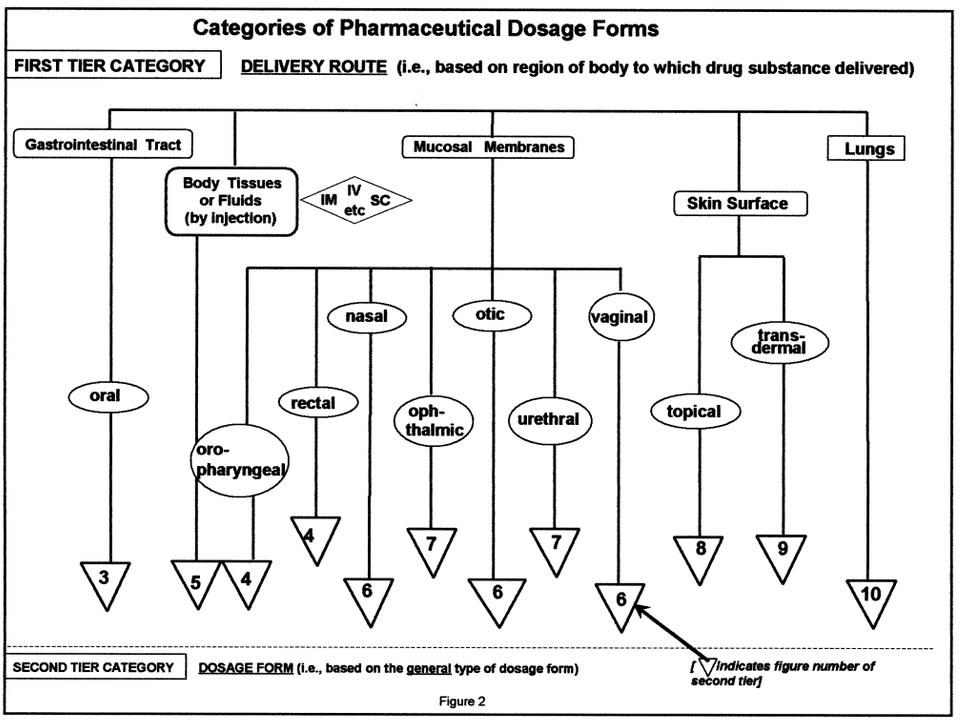

Figure 2

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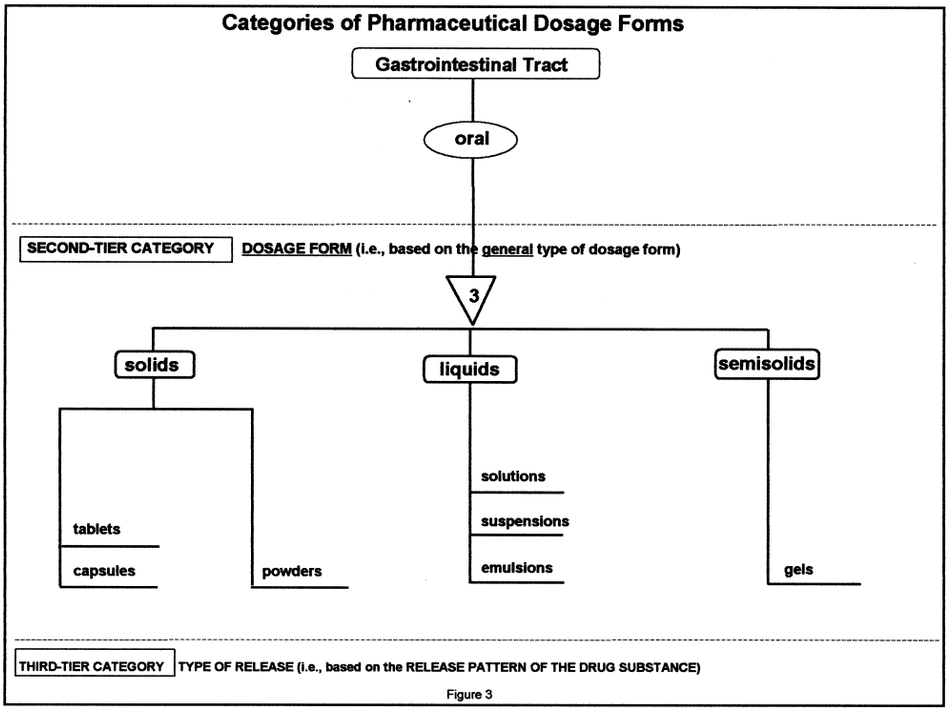


Figure 3

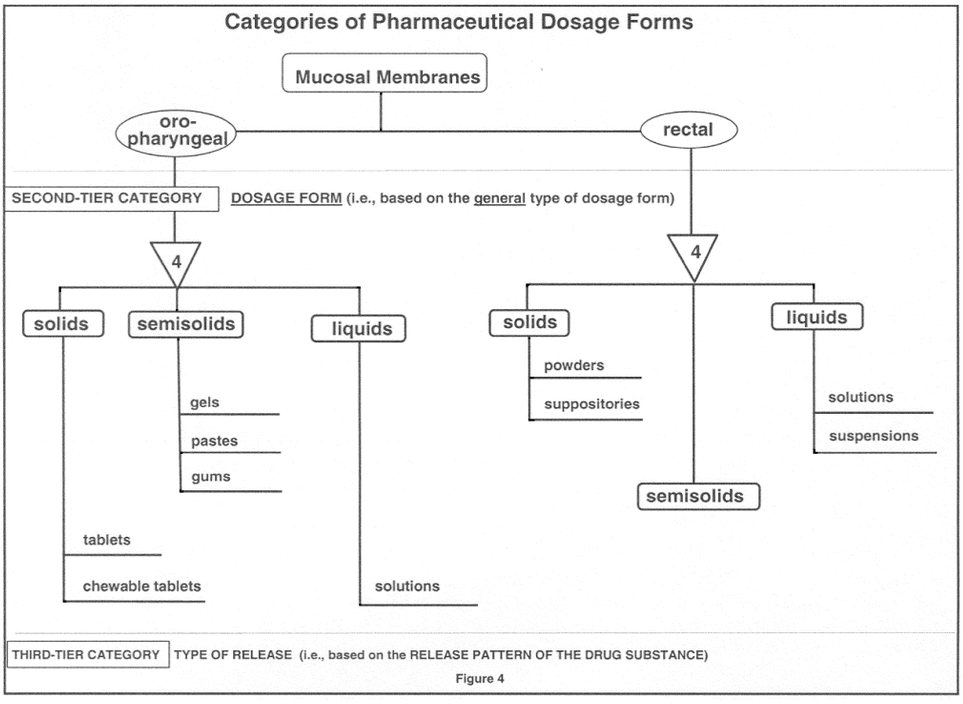
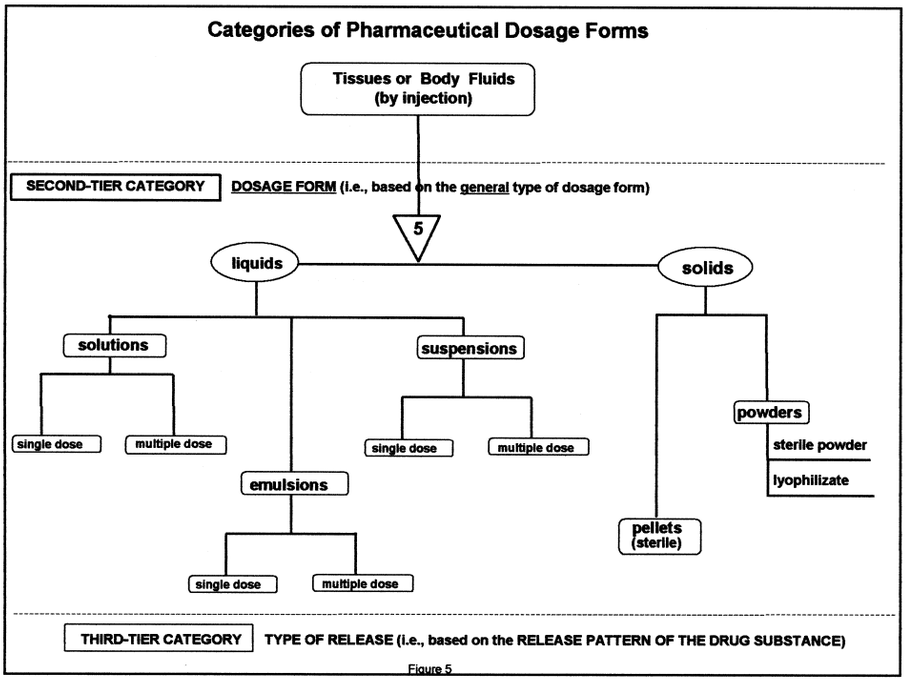


Figure 4



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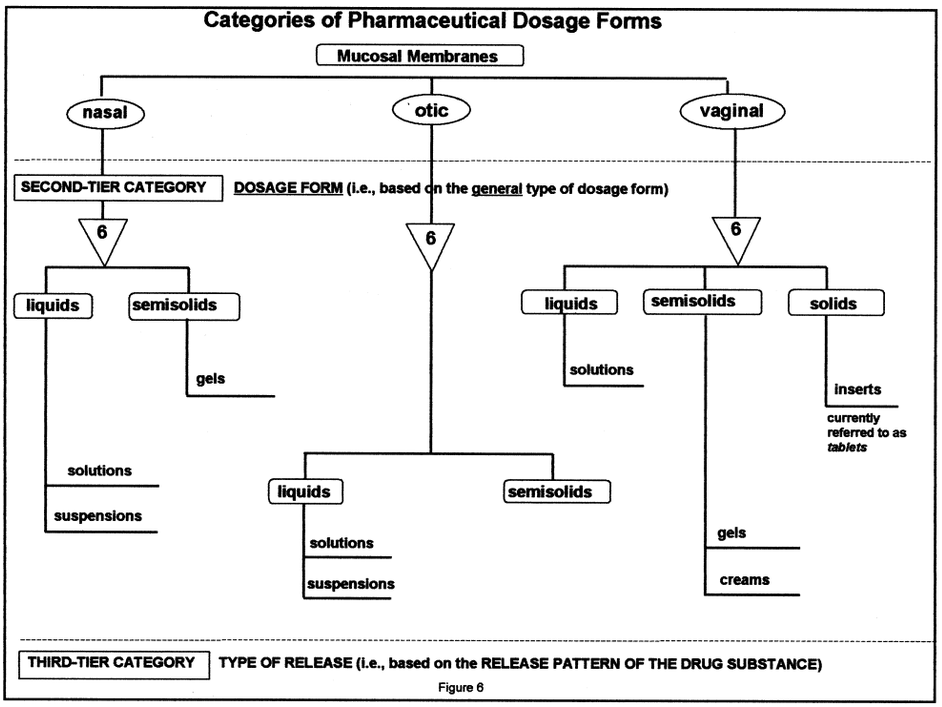

Figure 6

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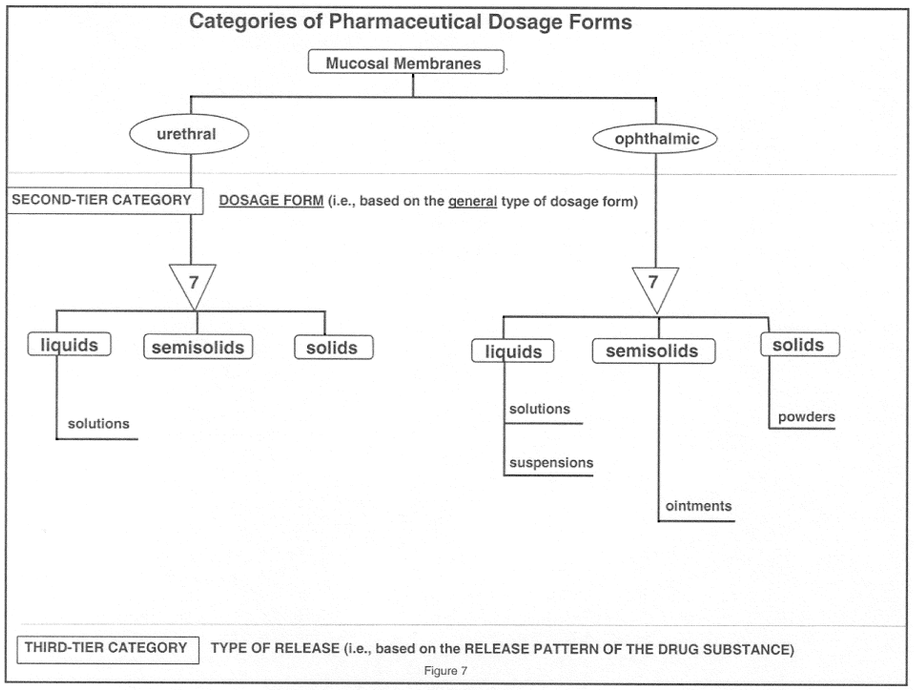

Figure 7

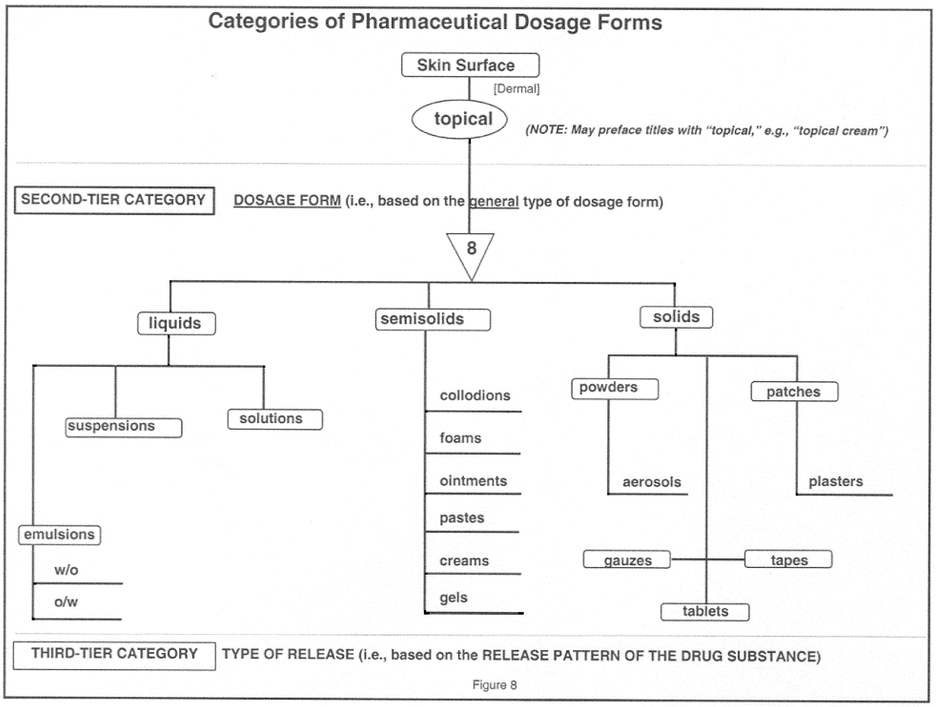

Figure 8

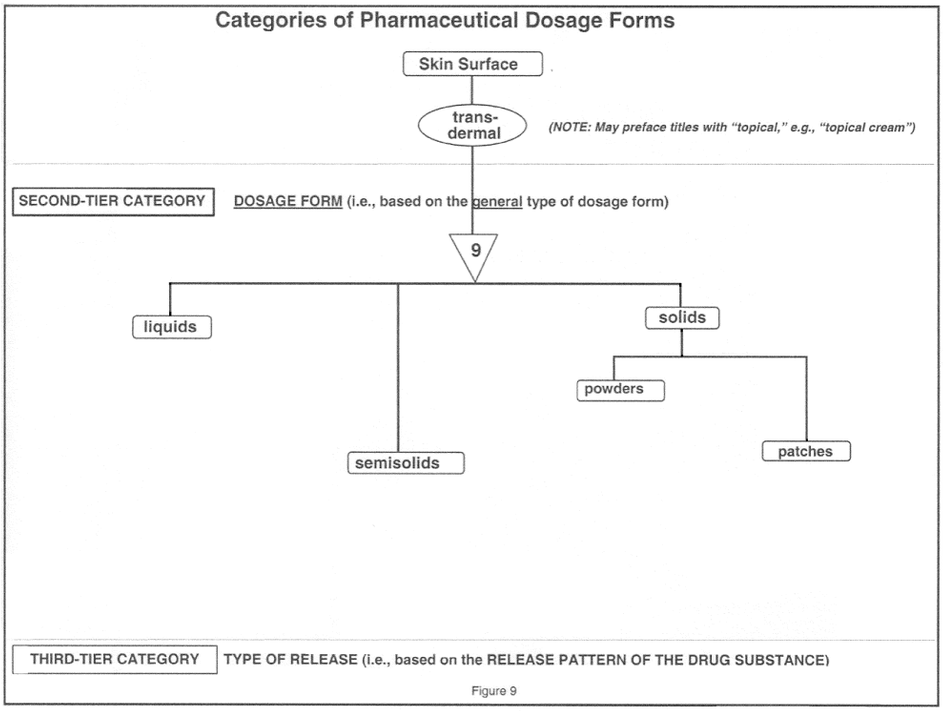

Figure 9

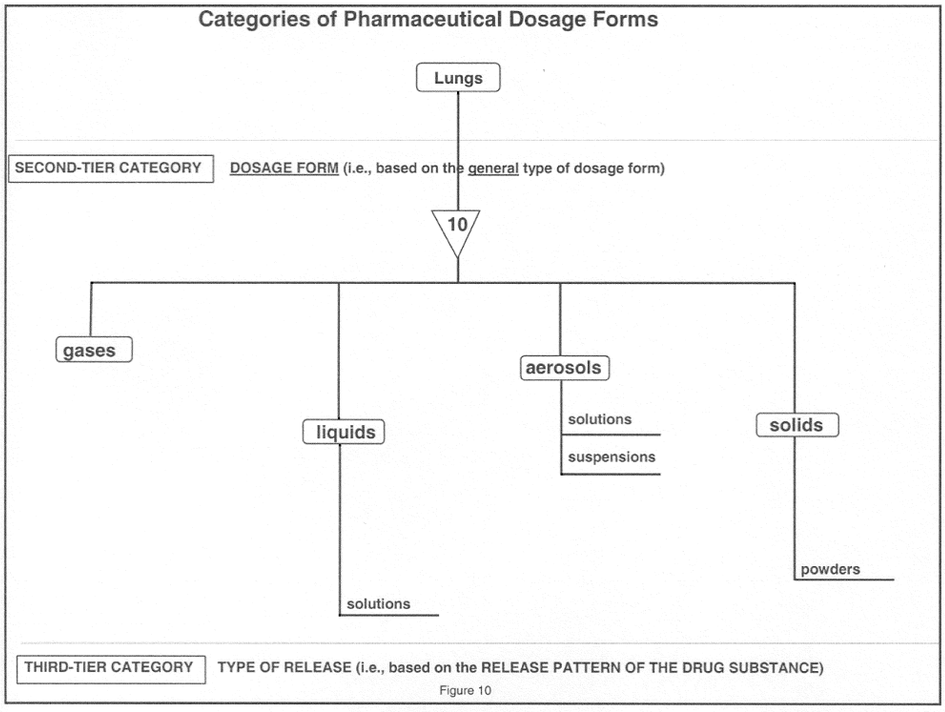

Figure 10

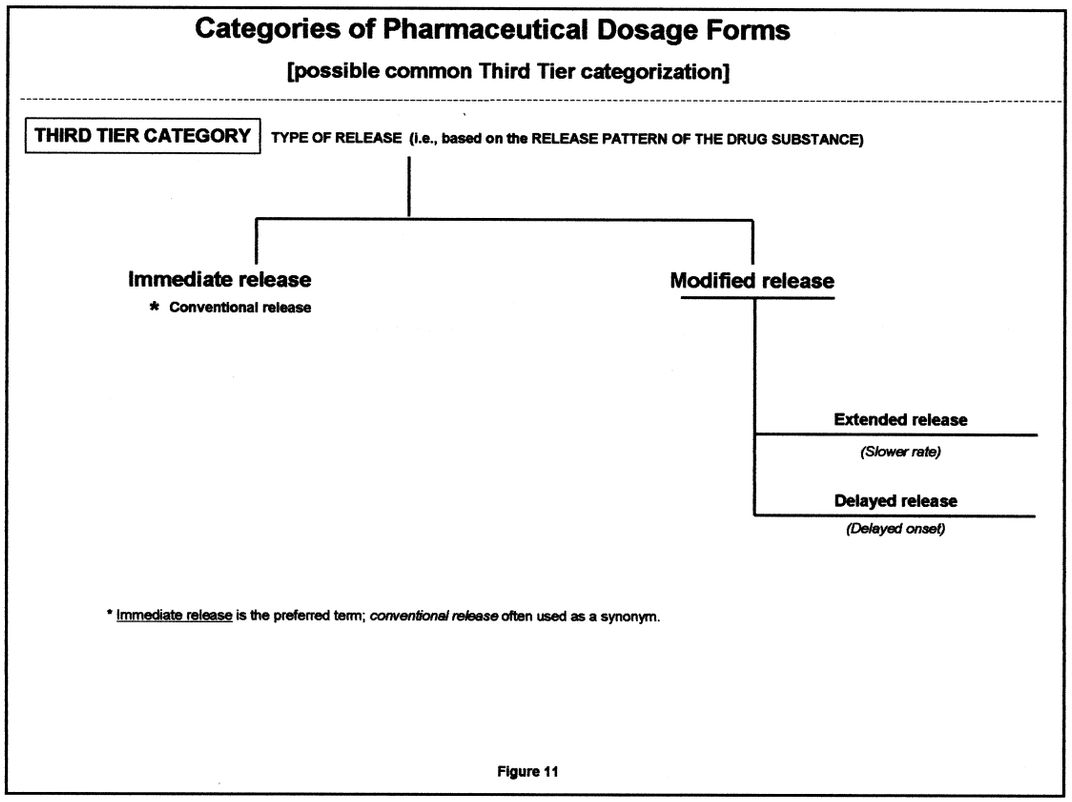

Figure 11

GLOSSARY

PART 1

AEROSOL
A product that is packaged under pressure and contains active ingredients that are released upon activation of an appropriate valve system.

CAPSULE
A solid dosage form in which the active, with or without other ingredients, is filled into either a hard or soft shell. Most capsule shells are composed mainly of gelatin.

CHEWABLE
Term applied to a dosage form that is intended to be chewed in the mouth before swallowing.

COLLODION
Liquid preparation composed of pyroxilin dissolved in a solvent mixture of alcohol and ether and applied externally.

CONCENTRATE
A dosage form that is intended to be diluted with a vehicle before use. This term is being phased out of USP titles.

CREAM
A dosage form comprising a viscous semisolid emulsion.

DELAYED RELEASE
Release pattern of the active from the dosage form is deliberately modified to delay release of the active for some period of time after initial administration.

DENTAL
Term applied to a dosage form that is applied to the teeth and/or gums for localized action.

EFFERVESCENT
Term applied to a dosage form, frequently tablets, containing ingredients that, when in contact with water, rapidly release carbon dioxide. The dosage form is dissolved or dispersed in water before administration.

EMULSION
A two-phase system in which one liquid is dispersed throughout another liquid in the form of small droplets. When an aqueous solution is the continuous phase, the system is designated an oil-in-water emulsion. Conversely, when oil is the continuous phase, the system is designated a water-in-oil emulsion.

EXTENDED RELEASE
Release pattern of the active from the dosage form is deliberately modified to slow down the rate of release compared to that of a conventional (immediate-release) form of the same active. The term is synonymous with *PROLONGED RELEASE*.

FOAM
An emulsion packaged in pressurized aerosol containers; when dispensed it has a fluffy, semisolid consistency.

GEL
A dispersion of small inorganic particles or a solution of large organic molecules rendered jellylike in consistency.

GUM
A dosage form in which the base consists of a plastically deforming material that, when chewed, releases the active into the oral cavity.

IMMEDIATE RELEASE
Synonymous with *CONVENTIONAL RELEASE* (see Part 2), i.e., the release pattern of active from a dosage form in which no deliberate effort has been made to modify the rate. In the case of capsules and tablets, the inclusion or exclusion of a disintegrating agent is not interpreted as a modification. *IMMEDIATE RELEASE* is the preferred term.

INHALATION
A dosage form designed to be dispersed in a current of air and drawn into the airways when the patient breathes in.

INJECTION (INJECTABLE)
A sterile dosage form injected into a body cavity, fluid, or tissue.

INSERT
A solid dosage form which is inserted into a body cavity, such as the urethra or vagina. See also *SUPPOSITORY*, a term used to describe inserts into the rectal region.

IRRIGATION
A sterile solution intended to bathe or flush open wounds or body cavities.

INTRAOCULAR
A sterile liquid dosage form for administration within the eye.

JELLY
Term synonymous with *GEL*.

LOZENGE
A solid dosage form intended to disintegrate or dissolve slowly in the mouth and usually prepared by compaction in a manner similar to that of tablets or by a molding process.

MODIFIED RELEASE
Release pattern of the active from the dosage form has been deliberately changed from that of a conventional (immediate-release) form of the same active.

NASAL
Term applied to a dosage form administered to the nasal cavity for local or systemic effect.

OCULAR
See *INTRAOCULAR*.

OIL
A liquid or liquefiable-on-warming solid that is insoluble in water but soluble in ether.

OINTMENT
A viscous oleaginous or polymeric semisolid dosage form.

OPHTHALMIC
A sterile dosage form administered to the external parts of the eye.

ORAL
Term applied to dosage forms that are to be delivered into the mouth and are often swallowed.

ORALLY DISINTEGRATING
A solid oral dosage form that disintegrates rapidly in the mouth.

OTIC
Term for dosage forms to be administered to, or by way of, the ear. Sometimes referred to as AURAL (see Part 2).

PASTE
A semisolid preparation with a stiff consistency containing a relatively high concentration of solids.

PELLET
A solid dosage form of a granular or regular shape.

PLASTER
A solid or semisolid mass supplied on a backing material and intended to provide prolonged contact with the skin.

POWDER
A solid, or mixture of solids, that has been reduced to a finely divided state.

RECTAL
Term applied to dosage forms that are to be delivered into the rectal region to provide local or systemic effect.

RINSE
A solution used to cleanse by flushing.

SHAMPOO
A solution or suspension used to clean the hair and scalp.

SOAP
The alkali salt(s) of a fatty acid or mixture of fatty acids.

SOLUTION
A liquid preparation that contains one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents.

SUBLINGUAL
A term applied to a dosage form that is intended to be placed underneath the tongue and to release the active for absorption in that region.

SUPPOSITORY
A solid dosage form in which one or more actives is dispersed in a suitable base and molded or otherwise formed into a suitable shape for insertion into the rectal area to provide local or systemic effect.

SUSPENSION
A liquid preparation that consists of solid particles dispersed throughout a liquid phase in which the particles are not soluble.

TABLET
A solid dosage form prepared from a powder or mixture of powders by compaction, by molding, or by means of lyophilization.

TINCTURE
An alcoholic or hydroalcoholic solution prepared from vegetable materials or from chemical substances.

TOPICAL
Term applied to dosage forms that are intended to be applied to the outer surface of the body.

VAGINAL
Term applied to solid dosage forms administered to the vagina, typically to obtain local effect.

PART 2

AROMATIC WATER
A clear, saturated aqueous solution of volatile oils or other aromatic or volatile substances.

AURAL (Auricular)
An unofficial alternative to *OTIC* (see Part 1) for administration to, or by way of, the ear.

BEAD
A solid dosage form in the shape of a small sphere. In most products a unit dose would consist of multiple beads. (See also *PELLETS*.)

COATED
Term applied to a solid dosage form that is covered by deposition of an outer solid that is different in composition from the core material.

CONVENTIONAL RELEASE
Release pattern of active from a dosage form in which no deliberate effort has been made to modify the rate. In the case of capsules and tablets, the inclusion, or exclusion, of a disintegrating agent is not interpreted as a modification. *IMMEDIATE RELEASE* (see Part 1) is synonymous with this term.

ELIXIR
A clear, pleasantly flavored, sweetened hydroalcoholic liquid containing dissolved actives intended for oral use. The term is no longer used in *USP–NF* (see Part 1 [ORAL][SOLUTION] or [ORAL][SUSPENSION]).

EMOLLIENT
A bland, fatty, or oleaginous substance applied locally to the skin to increase the tissue moisture content.

EXCIPIENT
An ingredient of a dosage form other than an active.

GRANULES
Preparations composed of dry aggregates of powder particles that may contain one or more actives, with or without other ingredients. They may be swallowed as such, or dispersed or dissolved in water. Granules are frequently compacted into tablets, with or without additional ingredients.

HARD-SHELL CAPSULE
A solid dosage form in which one or more actives, with or without other ingredients, is filled into a two-piece shell. Most hard-shell capsules are composed mainly of gelatin and are fabricated prior to the filling operation (see *CAPSULES* in Part 1).

LOTION
A fluid suspension or emulsion applied to the outer surface of the body. The term is no longer used in *USP–NF* (see Part 1 [TOPICAL][EMULSION] or [TOPICAL][SUSPENSION] or [TOPICAL][SOLUTION]).

MOLDED TABLET
A tablet that has been formed by dampening the ingredients and pressing them into a mold, then removing and drying the resulting solid mass.

MOUTHWASH
Term applied to an aqueous solution used to rinse the oral cavity.

ORO-PHARYNGEAL
Term applied to dosage forms in which the active is released into the buccal cavity and/or pharyngeal region to exert a local or systemic effect.

PILL
A solid spherical pharmaceutical dosage form, usually prepared by a wet massing technique. The use of the term *PILL* to describe tablets or capsules is discouraged.

SPIRIT
A liquid dosage form comprised of an alcoholic or hydroalcoholic solution of volatile substances.

STRIP
A dosage form or device in the shape of a long, narrow, thin solid material.

SYRUP
A solution containing high concentrations of sucrose or other sugars. The term is no longer used in *USP–NF (*see Part 1 [ORAL][SOLUTION] or [ORAL][SUSPENSION]).

TAPE
A dosage form or device in the shape of a long, narrow, solid material, frequently constructed of plastic or fabric.

TROCHE
A solid dosage form intended to disintegrate or dissolve slowly in the mouth and usually prepared by compaction in a manner similar to that of tablets. Also frequently referred to as *LOZENGE* (see Part 1).

URETHRAL
A term applied to a dosage form intended for insertion into the urethra to provide a local effect of the contained active.

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A New Technique for Amino Acid Analysis in Pharmaceutical Samples

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ABSTRACT In this report, we discuss principles and applications of a new technique for amino acid analysis. The technique utilizes anion-exchange chromatography in combination with integrated pulsed amperometric detection (IPAD) using a gold electrode. All organic anions carrying primary and secondary amino groups and hydroxyl groups are detected. The technique does not require any form of derivatization for making the analytes detectable. The detection limits are comparable to those obtained by fluorescence detection of amino acid derivatives.

The new method is effective for monitoring the level of nutrients in cell cultures, and it also has been applied to different types of protein and peptide hydrolysates. Additionally, this report provides suggestions for method validation following regulatory guidelines.

INTRODUCTION

Until very recently, all analytical techniques for amino acid analysis utilized either a cation-exchange separation with postcolumn derivatization followed by optical detection or prechromatographic sample derivatization with reversed-phase separation and one form or another of optical detection *(1)*. The new technique discussed here is distinctly different from other methods of amino acid analysis because it combines anion exchange with an entirely new detection technique, integrated pulsed amperometric detection (IPAD) *(2)*.

Anion-exchange separations of amino acids are carried out under relatively highly alkaline conditions (pH >12). Along with the amino acids, several other classes of compounds that are capable of forming anions at high pH are also separated, for example, mono-, di-, and oligosaccharides and amino sugars. The elution sequence is essentially a reversal of that obtained by cation exchange and is also markedly different from elution orders of derivatized amino acids on reversed-phase columns.

IPAD is carried out in a three-electrode detection cell. The detection potentials are applied between the gold surface and glass/silver–silver chloride combination electrode. Electrons that are transferred to the gold surface during the oxidation of analytes give rise to an electric current between the gold electrode and counter electrode. The use of two additional separate electrodes instead of a single reference electrode (reference and counter electrode) helps minimize the flow of electric current through the reference electrode and keeps the reference potential stable over a long period of time. If the main portion of the current is allowed to pass through the reference electrode, it causes the silver chloride to dissolve from the surface of the silver wire and, consequently, causes the potential of the reference electrode to vary. The current resulting from analyte oxidation at the gold electrode is measured by integration over a time period. The units of the detection signal are nanocoulombs (coulomb = ampere · second) rather than amperes.

The method does not require any derivatization of amino acids and achieves sensitivities (signal intensity at a given concentration) that are comparable to those obtained by fluorescence detection of various amino acid and carbohydrate derivatives.

It is important to note that routine use of a new detection technique engenders a new set of requirements. Some of these may be unfamiliar to even experienced users of derivatization-based detection techniques for amino acids. In addition to a general description of the new technique, this report provides guidelines for successful startup, routine operation, and validation of anion-exchange/IPAD systems.

EXPERIMENTAL

Anion Exchange of Amino Acids

All separations are achieved by ternary gradients employing three eluents (A: water, B: 0.25 M NaOH, and C: 1.0 M Na-acetate). A typical gradient program used for analyzing cell culture samples is shown in *Table 1a*.

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Table 1a: Typical Gradient Conditions for Analyzing Amino Acids in Cell Culture Samples (flow rate: 0.25 mL/min).

Time (min)	%E1	%E2	%E3	Curve	Comments
Init	94	6	0		Autosampler fills the sample loop
0.00	94	6	0		Valve from Load to Inject
2	94	6	0		Begin hydroxide gradient; valve from Inject to Load
11	64	36	0		Begin acetate gradient
18	40	20	40	8	
21	44	16	40	5	
23	14	16	70	8	
50	14	16	70		
50.1	20	80	0	5	Column wash with hydroxide
52.1	20	80	0		
52.2	94	6	0	5	Start of re-equilibration to initial conditions
75	94	6	0		

The high pH–stable anion-exchange columns are typically used as a combination of a guard (2 mm internal diameter × 50 mm length) and an analytical column (2 mm internal diameter × 250 mm length). The columns are packed with 9-µm-diameter microporous resin beads consisting of ethylvinylbenzene crosslinked with 55% divinylbenzene. The latex layer agglomerated on the surface of the 9-µm-diameter beads consists of 200-nm vinylbenzylchloride-based spherical particles functionalized with a mix of quaternary/tertiary ammonium groups. This mix of functionalized groups has a controlled ratio to give required selectivity for the separation of amino acids. The small particle size of the anion-exchange resin beads exhibits adequate mass transfer characteristics to enable good chromatographic peak efficiency. The highly cross-linked core of the packing permits the use of organic solvents to facilitate column cleanup.

Integrated Pulsed Amperometric Detection

The rapidly cycled sequence of potentials (IPAD waveform) applied to the three-electrode, low dead volume chromatographic detection cell is shown in *Table 1b*. The detection current is measured by integration over a time period also indicated in *Table 1b*.

Table 1b: IPAD Waveform

Time (s)	Potential vs pH	Integration
0.00	+0.13	
0.04	+0.13	
0.05	+0.28	
0.11	+0.28	Begin
0.12	+0.55	
0.41	+0.55	
0.42	+0.28	
0.56	+0.28	End
0.57	–1.67	
0.58	–1.67	
0.59	+0.93	
0.60	+0.13	

Indicator electrode: gold 1-mm diameter
Reference electrode: pH/Ag/AgCl
Counter electrode: titanium

Amino Acid Analysis System

A typical system fulfilling all of the requirements for anion-exchange/IPAD analysis of amino acids includes an autosampler, a column thermostat (the separation temperature has to be controlled within ±1 °C; for the majority of existing methods the prescribed temperature is 30 °C), microbore version of a gradient pump, and a suitable electrochemical detector for pulsed electrochemical detection. The detector should include a microbore-compatible three-electrode cell comprising a working electrode (gold), a reference electrode (pH), and a counter electrode. For automatic operation, a PC with appropriate system and data acquisition software should also be included.

Eluents and Standards

Use sterile vacuum filtration units with 0.2-µm Nylon filters for the filtration of all eluents. Blanket all eluents with inert gas at all times during preparation and use.

Eluent E1: Deionized Water

Filter the pure deionized water through 0.2-µm Nylon filters; then transfer into an eluent bottle. Seal the filtered water immediately. Minimize the contact time of the water surface with the atmosphere.

Eluent E2: 250 mM Sodium Hydroxide

The first step in the preparation of sodium hydroxide eluent is degassing and filtration of water (typically 1.0 L). Using a pipette, add an aliquot of 50% (w/w) sodium hydroxide (13.1 mL/L of water). Seal the container immediately after the sodium hydroxide transfer is complete. Minimize the carbon dioxide absorption during the transfer into the system eluent container, and apply inert gas immediately after transfer.

Eluent E3: 1.0 M Sodium Acetate

Dissolve 82.04 g of anhydrous sodium acetate in approximately 750 mL water. Seal the container during the dissolution step. Make up to 1.0 L with water, and filter through a 0.2-µm Nylon filter. Transfer the filtered sodium acetate eluent into the system eluent container.

Diluent Solutions Containing Sodium Azide

Prepare 1 L of a solution containing 20 mg/L of NaN_3. Use the solution without norleucine if the presence of an internal standard is not required. Store the pure azide solution in a closed container at room temperature.

Amino Acid Standards

Dissolve suitable amino acid standards and dilute with the diluent to obtain a solution that contains 5 µM or 10 µM of each amino acid. The standard solutions thus prepared remain stable for weeks if stored in a refrigerator. Sodium azide introduced with the diluent stabilizes diluted standards for up to 48 hours at room temperature. Suitable standard solutions of mono- and disaccharides may be added to the amino acid analysis standard solution, if and as necessary.

APPLICATIONS

Cell culture monitoring is perhaps one of the most important applications for the new amino acid analysis technique. In many cases, the technique makes possible a simultaneous quantitative determination not only of amino acids but also of sugars present in the medium *(3–4)*.

A typical chromatogram is shown in *Figure 1a*. The figure shows an overlay of chromatograms of a 1:50 diluted cell culture sample and of a mixture of amino acid standards to which glucose and sucrose were added in approximately the same concentration as the amino acids. The molar concentrations of the two sugars in the cell culture sample are about 100-fold higher than those of the amino acids. The chromatogram in *Figure 1a* represents roughly the highest possible excess of carbohydrates for such samples at which it is still possible to obtain quantitative results for the two carbohydrates and the full range of amino acids present.

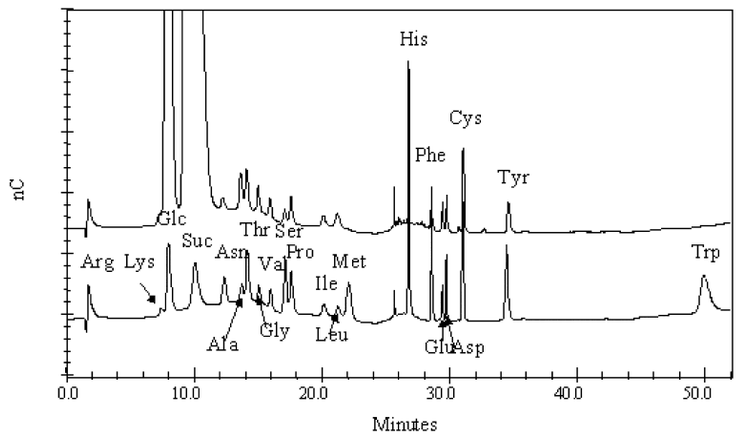

Fig. 1a: Overlay of a 1:50 diluted cell culture sample and amino acid standard (NIST SRM 2389, 321.5-fold diluted and containing glucose and sucrose at 8 M each) chromatograms. Injection volume: 25 µL. Gradient conditions: *Table 1a*. Detection waveform: *Table 1b.* Column temperature 30 °C. See Experimental for further details.

The resolution between the carbohydrates and the nearest peaks of amino acids can be optimized with the help of retention maps such as the one shown in *Figure 1b*. The "Initial NaOH Concentration" is the mobile phase composition during the first two minutes of the gradient of *Table 1a*. The resolution under the exact conditions of the *Table 1a* gradient is thus represented in *Figure 1b* by the data points at 15 mM of NaOH. As the initial mobile phase composition is decreased from 25 to 10 mM, the retention times of the nearest amino acids diverge, while the retention times of carbohydrates converge. Such a converging pattern for the retention times is observed for virtually all carbohydrates.

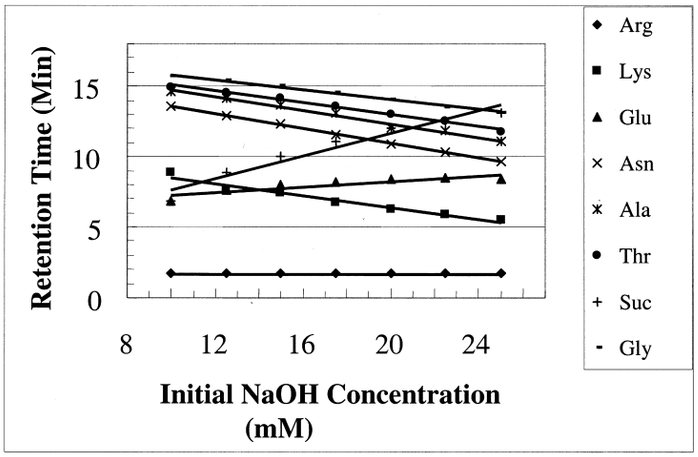

Fig. 1b: The Retention Map of two sugars and the nearest peaks of amino acids. Initial (0–2 min) concentration of sodium hydroxide of *Table 1a* is being changed between 25 and 10 mM. The timing and compositions of all other steps remain unchanged. The retention times of the peaks in the second half of the separation (His to Trp) are not affected. Also not changed is the total run time of 75 min (includes re-equilibration to initial gradient conditions).

At the initial concentration of 10 mM, the gap between the peaks of lysine and arginine becomes sufficiently wide that a full simultaneous separation of fucose, galactosamine, glucosamine, galactose, glucose, and mannose becomes possible (data not shown). Further developments of simultaneous carbohydrate and amino acid separations have been published *(5)*. Samples containing higher than approximately 100-fold molar excess of carbohydrates over amino acids require sample preparation that involves reducing the carbohydrate content prior to amino acid separation. A method describing an automated removal of carbohydrates from carbohydrate-rich amino acid samples has been re-

ported *(6)*, and the corresponding accessory consisting of an additional pump, valve, and cation-exchange cartridge is commercially available.

Another area of application of the anion-exchange/IPAD method is the analysis of hydrolysates of peptides and proteins. The method has been evaluated for different types of protein and peptide hydrolysates that are currently in use (HCl, MSA, MSA with performic acid oxidation, NaOH, propionic acid/HCl, etc.). The corresponding experimental protocols have been made available in a chapter of a recently published book *(7)*. A new validation protocol for protein hydrolysates analyzed by anion-exchange/IPAD is reported in a chapter of another book *(8)*.

An overlay of the amino acid standard and the peptide hydrolysate chromatograms is shown in *Figure 2*. As with many other amino acid analysis techniques, norleucine is used as an internal standard. Cysteic acid was added to the standard mixture to indicate the position of the peak in hydrolysate samples oxidized by performic acid. Occasionally, the arginine peak may co-elute closely with unretained "IPAD-positive" compounds such as non-anionic amines, e.g., tris(hydroxymethyl)-aminomethane, etc., as simulated by the addition of tris(hydroxymethyl)-aminomethane (TRIS) to the standard mixture in *Figure 2*. In those cases when reliable quantitation of arginine is impossible, users have the option to adjust the arginine retention and with it the resolution of the corresponding peak from the matrix. Complete separation of arginine is accomplished by adjusting the acidity during the reconstitution of hydrolysate samples following the evaporative centrifugation step after acid hydrolysis or by timed insertion of an acidic segment during the chromatographic separation *(9)*.

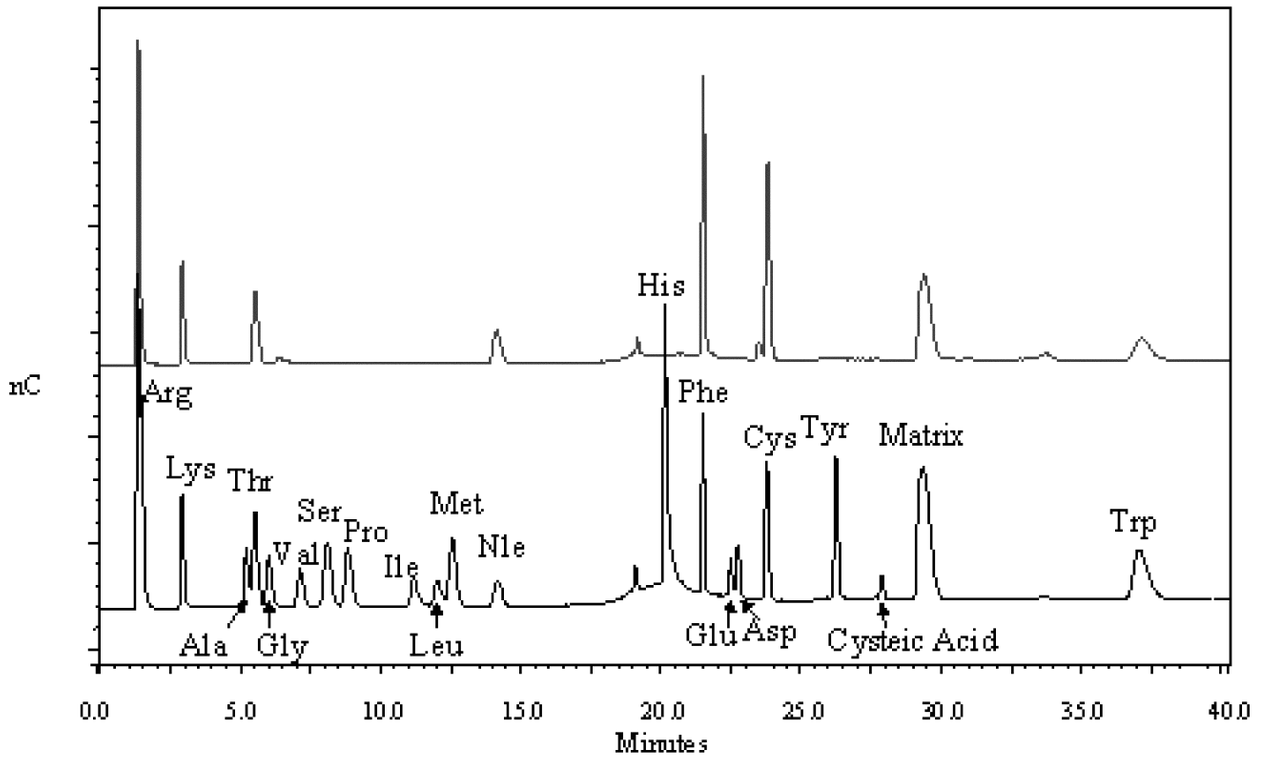

Fig. 2: Chromatograms of an NIST SRM 2389 (312.5-fold diluted) standard and peptide hydrolysate sample. Injection volume: 25 µL. Gradient conditions were the same as in *Table 1a*, except for the initial concentration of sodium hydroxide that was set at 60 mM between 0 and 2 minutes. The detection waveform and all other chromatographic conditions were the same as in *Fig. 1a*. The total amount of the original peptide used to generate the chromatogram was 0.754 µg. The hydrolysis was carried out in constant boiling HCl at 130 °C for 16 h.

The list of other useful examples of application of the anion-exchange/IPAD-based technique for amino acid analysis includes pharmaceutical excipient solutions, plant and soil extracts, food analysis, etc.

EXPERIMENTAL CONSIDERATIONS

Certain significant requirements of this new technique and the analyzer may not be immediately obvious even to experienced users of other types of amino acid analyzers. First is the requirement for sterility of eluents. Even small traces of bacterial contamination in eluents, eluent containers, eluent tubing, or glassware for eluent preparation may cause elevated detection backgrounds, interfering peaks, and excessive baseline rise during gradients. Bacterial contamination introduced, for example, by accidental skin contact, shared glassware, and eluents that were not passed through a 0.2-µm Nylon filter requires cleaning of the entire system by 2 N sodium hydroxide. Experienced users often add a low concentration of sodium hydroxide (10–25 mM) to the two non-hydroxide eluents (water and sodium acetate). This minimizes the effect of bacterial contamination and has been shown to eliminate the need for an occasional hydroxide cleanup.

The second of the requirements arises from the sensitivity of the detection methods for hydroxylic compounds. Accidental contamination of eluents by sugars or some organic solvents may affect the long-term stability of detector response and may require a thorough system cleanup with 6 N nitric acid. Incorrect eluent filtration materials such as cellulose acetate or inadvertent introduction of alcohols from the autosampler rinsing fluid that contains 50% methanol have been identified as the two most frequent causes of system contamination by hydroxylic compounds.

The third of the unusual requirements is that of the absence of even traces of thiolic impurities in the eluents. Because of their affinity to gold, thiols can accumulate on the surface of the working electrode, causing a gradual decrease of the detection signal. The authors recommend frequent testing of detection response by injections of a single component standard such as histidine. Investigations show that thiol impurities are being introduced exclusively from contaminated lots of sodium acetate used in the preparation of eluents. Thus, using a thiol-free sodium acetate is absolutely critical for the new amino acid analysis technique.

The required system clean-up after accidental use of contaminated acetate consists of thorough rinsing of eluent tubing and column with a thiol-free, acetate-containing mobile phase. The working electrode has to be either replaced or reconditioned by polishing.

Because of these unique requirements, the use of a dedicated system for amino acid analysis is recommended. Any changeover between two or more chromatographic methods may require long and laborious cleanups. One possible exception is using the same system for carbohydrate analysis and amino acid analysis. Because the system requirements are very similar for both techniques (both use anion-exchange/IPAD), a changeover between columns optimized for carbohydrate and amino acid analyses is very easy.

METHOD VALIDATION

In this section we provide recommendations for method validation following the relevant regulatory guidelines *(10–11)*.

Accuracy

For accuracy testing with culture samples, the authors recommend spiking samples with an amino acid or sugar normally not present in that particular type of cell culture media. Norleucine, asparagine, fucose, galactose, and fructose are examples of possible test compounds for accuracy evaluation. Most cell culture samples have to be diluted at least 50-fold prior to analysis by the anion-exchange/IPAD method, and the spiking compound can be added with the diluent solution. Assay accuracy can thus be monitored with each injection. Also, as recommended in the ICH Guidelines *(11)*, accuracy can be inferred from precision, linearity, and specificity evaluation results. Additional data on the accuracy of this technique have been reported in Table 2 of Reference 2.

Precision

The specified precision (relative standard deviation, RSD) of the discussed method is 2 to 5% RSD within one day. An RSD of <10% is achievable over a period of several weeks. Sample stability, proper functioning of the autosampler, column performance within specifications, correct peak identification, and integration are the most important requirements for achieving satisfactory precision in amino acid analysis by the anion-exchange/IPAD method.

Sample stability

A solution of 20 mg/L of sodium azide is recommended as a matrix for all standards and samples. If bacterial contamination is minimized (e.g., gloves, sterile containers, azide diluent), standard solutions containing micromolar and picomolar amounts of amino acids have been found to be stable within the specified measurement error (2–5% RSD) for 3 days at room temperature. Over a longer period of time, for example 5–7 days, some of the less stable amino acids such as, e.g., arginine, may exhibit 5–10% decrease in concentration. The majority of the standard amino acids, however, are stable over 5–7 days even at room temperature.

Autosampler functioning

One should neither under- nor over-fill the autosampler vials. Operators should re-prime the sample syringe if they observe air bubbles inside the rinse line or in the sample syringe, and they should tighten up connections leading to the sample syringe valves if they observe air bubbles inside the Teflon tubing leading from the syringe to the injection port. The authors recommend using 20 mg/L sodium azide as an autosampler rinse solution.

Column performance

Deteriorating column performance may degrade the resolution of several peak pairs. The affected peaks can be frequently misidentified or incorrectly (and irreproducibly) integrated in the automatic mode. In the majority of cases, separation performance can be restored by replacing the guard column, modifying the gradient method, correcting the setting of the column thermostat, or adjusting the sample matrix. The most important critical pairs to watch are alanine/threonine in the alanine-threonine-glycine triplet, leucine/methionine in the isoleucine-leucine-methionine triplet, and glutamate/aspartate in the glutamate-aspartate doublet.

The alanine/threonine peak pair is the one most affected by a deteriorated guard column. It is not unusual to replace the guard column several times during a lifetime of an analytical column (6–24 months). A lower degree of resolution between alanine and threonine is frequently observed with gradients optimized for simultaneous carbohydrate-amino acid separations *(Figure 1a)*. If necessary, users have an option to apply on-line carbohydrate removal *(6)* in connection with one of the gradient methods optimized for the separations of carbohydrate-free amino acid mixtures. This approach always improves the resolution of the alanine/threonine peak pair. Poor resolution of the leucine/methionine pair usually indicates incorrect column thermostat temperature. Only a slight deviation from the prescribed column temperature of 30 °C affects the resolution of these two peaks while the resolution of all other amino acid peaks remains unaffected. The effect of column temperature on the resolution of amino acids, particularly of the leucine/methionine pair, and techniques to improve leucine/methionine resolution have been discussed *(12)*.

A decrease in glutamate/aspartate resolution is observed if the matrix of the injected samples is too acidic or if the ionic strength is too high. Consequently, the authors recommended not exceeding ~0.1 M concentration of mineral acids or salts in the analyzed samples.

Correct peak identification and integration

Incorrect integration can cause high RSD even if all the modules are functioning perfectly. Such a situation is easily diagnosed by creating an overlay of several injections of the same standard. If the overlay of five or more peaks has the appearance of seemingly merging into a single chromatogram and the RSD is still higher than 5%, incorrect integration is the most likely cause of the problem.

Analysts can review the position of baseline and integration markers in each chromatogram and reposition the peak delimiters, if necessary. Should the high value of RSD result from peak misidentification, one can readjust the retention time intervals for the affected peaks using the chromatographic software.

Specificity

This method for amino acid analysis relies on the combined use of ion-exchange separation and electrochemical detection, both of which are known as highly selective methods. Their combined use further enhances the achievable specificity. Following are examples of compounds that can be reliably handled by the method:

Compounds that are neither retained nor detected

All inorganic and organic cations (including ammonium, quaternary and tertiary ammonium, and transition metals); all organic molecules that are non-ionized and lack primary or secondary amine groups.

Compounds that are retained but not detected

All inorganic and organic anions (including phosphates, all alcohols, and carboxylates such as citric acid or EDTA).

Compounds that are not retained but detected

Sugar alcohols and ethanolamines (including TRIS). The nonretained "IPAD-positive" compounds, such as for example TRIS or myoinositol, can on occasions make the quantitation of arginine difficult or impossible. For such cases, the literature describes a modified protocol for achieving improved resolution of arginine *(9)*.

Compounds that are retained, detected, and separated depending on the ratio of molar concentrations

Sugars and amino sugars. Depending on molar concentration ratios and the specific pair of chromatographic peaks, sugars up to ~100-fold molar excess can be separated from the nearest co-eluting amino acid peak. An example of such a separation of excessive sugar concentrations from amino acids is illustrated in *Figure 1a*. For samples containing even higher molar ratios of sugar concentrations, an automated sugar-removal technique should be used *(6)*.

Impurity Testing

The IPAD detection technique for amino acid analysis offers a unique approach to verifying peak purity and detecting unresolved impurities co-eluting with peaks of interest. The method is described in *(4)*. IPAD detection makes it possible to generate peak area ratios obtained with different modes of electrode current integration. These ratios are compound specific. The unexpected values of peak ratios indicate the presence of an impurity or impurities.

Detection and Quantitation Limits

Table 2 documents detection limits calculated as 3:1 signal-to-noise ratios that are typical for the performance of the anion-exchange/IPAD technique (see column 2). Limit of quantitation data can be calculated as 10:1 signal-to-noise ratios from the same data.

Table 2: Summary of typical validation results

Amino Acid	Limit of Detection (pmol)	Linear Range (pmol)	R^2	RSD (%) 20 Runs
Arginine	0.11	2.5–500	0.9990	1.97
Lysine	0.22	2.5–500	0.9999	1.67
Alanine	0.39	2.5–500	0.9990	0.71
Threonine	0.19	2.5–2000	0.9993	0.67
Glycine	0.44	2.5–500	0.9997	1.34
Valine	0.44	2.5–1000	0.9993	0.73
Serine	0.28	2.5–2000	0.9993	0.84
Proline	0.29	2.5–1000	0.9996	1.38
Isoleucine	0.58	2.5–2000	1.0000	0.82
Leucine	0.67	2.5–2000	1.0000	1.10
Methionine	0.36	2.5–500	0.9999	0.75
Histidine	0.043	2.5–250	0.9909	0.88
Phenylalnine	0.10	2.5–500	0.9980	0.57
Glutamate	0.41	2.5–500	0.9995	1.51
Aspartate	0.22	2.5–500	0.9994	1.65
Cystine	0.050	2.5–500	0.9979	0.91
Tyrosine	0.093	2.5–500	0.9995	1.20

Linearity

The calibration plots for most amino acids are linear from their respective detection limits to 1 nmol (amount injected). The basic amino acids (Arg, His, Lys) represent an exception. Their calibration plots are linear up to several hundred pmol (amount injected).

A possibility exists for expanding the linear range for all amino acids at the cost of increasing the detection limits and decreasing sensitivity. This can be done by decreasing the waveform potential values at 0.12 and 0.42 sec (*Table 1b*) to a value between 0.5 to 0.28 V vs pH. The same potential value has to be selected for both time points of the waveform.

A representative example of linearity evaluation is shown in the third and fourth columns of *Table 2*. An in-depth discussion of aspects that influence the linearity of IPAD is presented in *(2)*, which also provides a detailed discussion about detection waveform optimization.

Range

Upper Limit

For the purpose of determining and documenting the upper limit of the (linearity) range, amino acids can be divided into three classes:

- aliphatic amino acids such as glycine, alanine, valine, isoleucine, and leucine
- basic amino acids such as arginine, lysine, and histidine
- hydroxy amino acids and sugars such as serine and threonine.

Aliphatic amino acids exhibit the broadest range of linearity, frequently exceeding 1 nmol injected. Their upper limits of detection are usually slightly higher than those of the other two groups. The upper limits of detection of basic amino acids are usually less than those of the other two groups.

The upper limit of linearity of the hydroxy amino acids and sugars may be slightly lower than that of the aliphatic amino acids. The ranges of amino acids carrying mercapto or thioether groups are similar to those of the hydroxy amino acids.

Lower Limit

The lower limit of the range is dictated by the relative position of a peak in the gradient separation. The peaks eluting at the final section of the acetate gradient tend to have lower detection limits than those eluting in isocratic regions or parts of the chromatogram eluted by hydroxide gradient. The peak position is a much more important factor in determining the lower detection limit than is the actual result of electrode response for the same peak. See, for example, the much higher response for histidine than for lysine. A similar comparison can also be made for leucine and alanine.

To make the documentation less confusing and to simplify the evaluation, it is thus possible to validate the amino acid analysis using the anion-exchange/IPAD method only for a group of well-selected amino acids. The worst-case scenario can be defined by selecting the data of, for example, lysine and leucine for the upper and lower limits of the range, respectively. All other results would either conform to or exceed such a specification. Alternatively, it is also possible to define a span from worst to best possible values for the upper and lower limits of the range. The selection of experimental values of leucine and threonine or histidine and threonine for the lower and upper limits, respectively, would seem appropriate.

Robustness

The effects of different compositions of gradients are illustrated in Tables 2, 3, and 4 and Figures 4, 5, 6, and 7 of Reference 12. The influence of temperature variations on the separation of 17 amino acids is shown in Figure 10 of Reference 12. Figure 16 of Reference 12 shows the effects of different autosampler injection modes on the quality and appearance of the chromatograms.

CONCLUSION

Anion-exchange/IPAD is a new technique for the analysis of un-derivatized amino acids and also of carbohydrates. Frequently, amino acids and sugars can be analyzed simultaneously if they are present in the same sample. The selectivity of separations can be modified to a very large degree by optimization of gradient-elution programs. The selectivity, linearity, and sensitivity of the detection response can be adjusted by choosing different detection potentials of the detection waveform. The evaluation results show anion-exchange/IPAD to be a useful technique for the analysis of cell culture media, protein hydrolysates, pharmaceutical excipients, and many other types of amino-acid–containing samples.

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Stimuli to the Revision Process

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

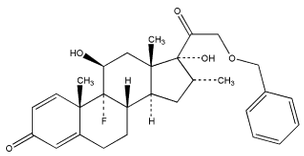
USP Dictionary of USAN and International Drug Names
2003 USP DICTIONARY SUPPLEMENT 3

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2003 edition of the USP Dictionary (USPD) up to date. The cumulative contents of the supplements to the current (2003) edition will be included in the next complete edition of the Dictionary.

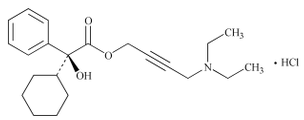
New United States Adopted Names (USAN)

The following are newly established United States Adopted Names (USAN). These names will not be listed cumulatively; see preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

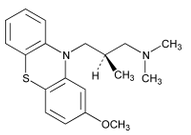
Dexamethasone Beloxil [*2003*] (dex a meth′ a sone bel ox′ il). $C_{29}H_{35}F_5$. 482.60. (1) (11β,16α)-9-Fluoro-3,17-dihydroxy-16-methyl-21-(phenylmethoxy)-pregna-1,4-diene-3,20-dione; (2) 21-(Benzyloxy)-9-fluoro-11β,17-dihydroxy-16α-methylpregna-1,4-diene-3,20-dione; (3) 21-*O*-Benzyldexamethasone. *CAS-150587-07-8*. *Anti-inflammatory used in the treatment of uveitis, iritis, keratitis, postsurgical inflammation, vernal keratoconjunctivitis, and giant papillary conjunctivitis.* (Alcon)



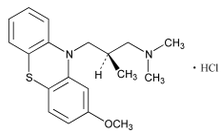
Esoxybutynin Chloride [*2003*] (es ox i bue′ ti nin). $C_{22}H_{31}NO_3$.HCl. 393.95. (1) Benzeneacetic acid, α-cyclohexyl-α-hydroxy-, 4-(diethylamino)-2-butynyl ester, hydrochloride, (α*S*)-; (2) 4-(Diethylamino)but-2-ynyl (2*S*)-cyclohexylhydroxyphenylacetate hydrochloride. *CAS-230949-16-3*. *Treats overactive bladder symptoms of urgency, frequency and urinary incontinence* (*antispasmodic/anticholinergic*). (Sepracor)



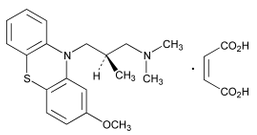
Levomepromazine [*2003*] (lee″ voe me proe′ ma zeen). $C_{19}H_{24}N_2OS$. 328.47. (1) 10*H*-Phenothiazine-10-propanamine, 2-methoxy-*N*,*N*,β-trimethyl-, (β*R*)-; (2) (–)-(2*R*)-3-(2-Methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine. *CAS-60-99-1*. INN; BAN; DCF. *Analgesic* (*central nervous system depressant*). Nozinan (Aventis); (Orgasynth) ✧*RP-7044; XP03*



Levomepromazine Hydrochloride [*2003*]. $C_{19}H_{24}N_2OS$.HCl. 364.93. (1) 10*H*-Phenothiazine-10-propanamine, 2-methoxy-*N*,*N*,β-trimethyl-, monohydrochloride, (β*R*)-; (2) (2*R*)-3-(2-Methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine hydrochloride. *CAS-1236-99-3*. JAN. *Analgesic* (*central nervous system depressant*) . Nozinan (Aventis); (Orgasynth)

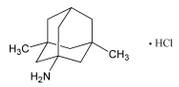


Levomepromazine Maleate [*2003*]. $C_{19}H_{24}N_2OS.C_4H_4O_4$. 444.54. (1) 10*H*-Phenothiazine-10-propanamine, 2-methoxy-*N*,*N*,β-trimethyl-, (β*R*)-, (2*Z*)-2-butenedioate (1:1); (2) (2*R*)-3-(2-Methoxy-10*H*-phenothiazin-10-yl)-*N*,*N*,2-trimethylpropan-1-amine hydrogen (2*Z*)-but-2-enedioate. *CAS-7104-38-3*. JAN. *Analgesic* (*central nervous system depressant*). Nozinan (Aventis); (Orgasynth); Tisercin (Elan)

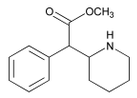


Lucinactant [*2003*] (loo sin ak′ tant). Lucinactant. A surfactant formulation containing a mixture of synthetic phospholipids, fatty acid, and synthetic peptide. Lucinactant is comprised of sinapultide, colfosceril palmitate (dipalmitoylphosphatidylcholine [DPPC]), palmitoyloleaylphosphatidyl glycerol, sodium salt (POPG), and palmitic acid.*Treatment of respiratory distress syndrome* (*RDS*) *in adults; treatment and prevention of RDS in infants.* (Acute Therapeutics) ✧*KL_4-surfactant; ATI 02*

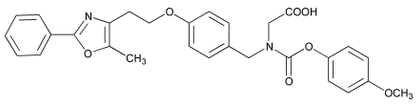
Memantine Hydrochloride [*2003*] (me man′ teen). $C_{12}H_{21}N.HCl$. 215.76. (1) Tricyclo[3.3.1.1^{3,7}]decan-1-amine, 3,5-dimethyl-, hydrochloride; (2) 3,5-Dimethyltricyclo[3.3.1.1^{3,7}]decan-1-amine hydrochloride; (3) 3,5-Dimethyl-1-adamantanamine hydrochloride; (4) 1-Amino-3,5-dimethyladamantane hydrochloride. *CAS-41100-52-1. Treatment of Alzheimer's disease.* Ebixa (Cambrex Profarmaco, Belgium); Axura (Cambrex Profarmaco, Belgium)



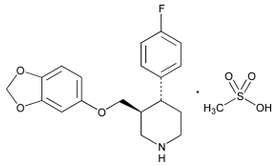
Methylphenidate [*2003*] (meth il fen′ i date). $C_{14}H_{19}NO_2$. 233.31. (1) 2-Piperidineacetic acid, α-phenyl-, methyl ester; (2) α-Phenyl-2-piperidineacetic acid methyl ester. *CAS-113-45-1*. INN; BAN. *Stimulant* (*CNS*). (Mallinckrodt)



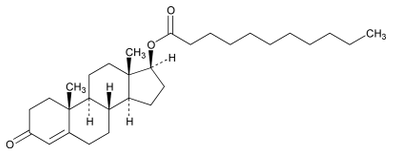
Muraglitazar [*2003*] (myoo ra gli′ ta zar). $C_{29}H_{28}N_2O_7$. 516.54. (1) Glycine,*N*-[(4-methoxyphenoxy)carbonyl]-*N*-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl]-; (2) [[(4-Methoxyphenoxy)carbonyl][4-[2-(5-methyl-2-phenyloxazol-4-yl)ethoxy]benzyl]amino]acetic acid. *CAS-331741-94-7* [free acid]. *Treatment of type-2 diabetes mellitus, mixed dyslipidemia, atherosclerosis, and metabolic syndrome* (*dual* (*alpha and gamma*) *peroxime proliferator activated* (*PPAR*) *agonist*). (Bristol-Myers Squibb) ✧*BMS-298585*



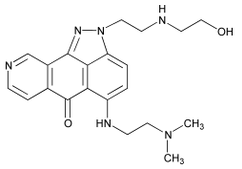
Paroxetine Mesylate [*2003*] (pa rox′ e teen). $C_{19}H_{20}FNO_3.CH_4O_4S$. 441.47. (1) Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, (3*S*,4*R*)-, methanesulfonate; (2) (–)-*trans*-4*R*-(4′-Fluorophenyl)-3*S*-[(3′,4′-methylenedioxyphenoxy)methyl]piperidine, mesylate. *CAS-217797-14-3*. *Treatment of major depressive disorder, obsessive compulsive disorder, and panic disorder* (*selective serotonin reuptake inhibitor*). Asimia (Heumann Pharma GmbH, Germany) ✧*POT.mes*



Testosterone Undecanoate [*2003*] (tes tos′ ter own un dek′ a noe′ ate). $C_{30}H_{48}O_3$. 456.70. (1) 3-Oxoandrost-4-en-17β-yl undecanoate; (2) Androst-4-en-3-one, 17-[(1-oxoundecyl)oxy]-(17β). *CAS-5949-44-0. In males: testosterone replacement therapy for primary or secondary hypogonadal disorders. In female-to-male transsexuals: masculinization. Moreover, in men, testosterone therapy may be indicated in osteoporosis caused by androgen deficiency.* Andriol (Diosynth B.V., Netherlands); Andriol (Organon) ✧*Org 538*



Topixantrone [*2003*] (toe pix′ an trone). $C_{21}H_{26}N_6O_2$. 394.47. (1) Indazolo[4,3-*gh*]isoquinolin-6(2*H*)-one, 5-[[2-(dimethylamino)ethyl]amino]-2-[2-[(2-hydroxyethyl)amino]ethyl]-; (2) 5-[[2-(Dimethylamino)ethyl]amino]-2-[2-[(2-hydroxyethyl)amino]ethyl]indazolo[4,3-*gh*]isoquinolin-6(2*H*)-one. *CAS-156090-18-5*. INN; BAN. *Anti-neoplastic.* (Novuspharma SpA) ✧*BBR 3576* (*dihydrochloride*)



Yttrium Y 90 Epratuzumab [*2003*] (it′ ree um e pra too′ zoo mab). (1) Immunoglobulin G1, anti-(human CD22 (antigen)) (human-mouse monoclonal hLL2 γ-chain), disulfide with human-mouse monoclonal hLL2 κ-chain, dimer, yttrium-90Y chelate; (2) Immunoglobulin G1 (human-mouse monoclonal hLL2 γ-chain anti-human antigen CD22), disulfide with human-mouse monoclonal hLL2 κ-chain, dimmer, yttrium-90Y chelate. Molecular weight is approximately 150,000 daltons. *CAS-501423-23-0. Radioimmunotherapy* (*RAIT*) *for non-Hodgkin's B-cell lymphoma patients* (*monoclonal antibody*). LymphoCide (Immunomedics) ✧^{90}*Y-hLL2*

Yttrium Y 90 Labetuzumab [*2003*] (it′ ree um la be too zoo′ mab). (1) Immunoglobulin G1, anti-(human carcinoembryonic antigen) (human-mouse monoclonal hMN-14 γ-chain), disulfide with human-mouse monoclonal hMN-14 κ-chain, dimer, yttrium-90Y chelate; (2) Immunoglobulin G1 (human-mouse monoclonal hMN-14 γ-chain anti-human carcinoembryonic antigen), disulfide with human-mouse monoclonal hMN-14 κ-chain, dimer, yttrium-90Y chelate. Molecular weight is approximately 150,000 daltons. *CAS-501423-27-4. Radioimmunotherapy* (*RAIT*) *of CEA-expressing tumors for use in the treatment of colorectal cancer* (*monoclonal antibody*). CEA-Cide (Immunomedics) ✧^{90}*Y-hMN-14*

Nomenclature

Revisions of United States Adopted Names (USAN)

The following are revisions of existing United States Adopted Names (USAN) and other names.

Aminosalicylic Acid

Delete the following:

[4-aminosalicylic acid]

Ceftazidime

Change the CAS number to read:

CAS-78439-06-2; CAS-72558-82-8 [anhydrous]

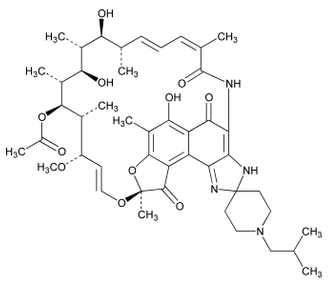
Meradimate

Change the second chemical name to read:

(2) Anthranilic acid, *p*-menth-3-yl ester

Rifabutin

Change the chemical structure to read:



Zinc Carbonate

Change the CAS number to read:

CAS-3486-35-9

Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Helath Organization (WHO).

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

Proposed International Nonproprietary Names

The following 43 names have been selected by the World Health Organization (WHO) as Proposed International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information*, Vol 17, No. 1, 2003.

Any comments or formal objections to the proposed names should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Proposed INN	Therapeutic Indication
Alvocidib	*Antineoplastic*
Anatibant	*Bradykinin B2 receptor antagonist*
Ardenermin	*Immunostimulant*
Arimoclomol	*Symptomatic antidiabetic agent*
Arundic Acid	*Neuroprotective agent*
Aselizumab	*Immunomodulator*
Asoprisnil Ecamate	*Progesterone receptor modulator*
Ataciguat	*Vasodilator*
Atazanavir	*Antiviral*
Atocalcitol	*Vitamin D analogue*
Barixibat	*Bile acid absorption inhibitor*
Barusiban	*Oxytocin antagonist*
Bertilimumab	*Immunomodulator*
Bortizomib	*Antineoplastic*
Cinacalcet	*Calcimimetic*
Darunavir	*Antiviral*
Dexmethylphenidate	*Sympathomimetic*
Disufenton Sodium	*Neuroprotective agent*
Dofequidar	*Antineoplastic*
Doramapimod	*Immunomodulator*
Etiprednol Dicloacetate	*Corticosteroid; anti-inflammatory*
Etavirine	*Antiviral*
Etriciguat	*Vasodilator*
Fipamezole	*Antiparkinsonian; α_2-adrenoreceptor antagonist*
Gemcabene	*Antihyperlipidaemic*
Ibrolipim	*Antiatherogenic*
Iclaprim	*Antibacterial*
Iosimenol	*Contrast medium*
Latidectin	*Antiparasitic*
Lurasidone	*Antipsychotic*
Mantabegron	*β_3-Adrenoreceptor agonist (veterinary drug)*
Matuzumab	*Immunomodulator*
Mitratapid	*Microsomal triglyceride transfer protein (MTP) inhibitor (veterinary drug)*
Oxeglitazar	*Antidiabetic*
Posizolid	*Antibacterial*
Rafabegron	*β_3-Adrenoreceptor agonist*
Rupintrivir	*Antiviral*
Salcaprozic Acid	*Absorption promotor*
Sorafenib	*Antineoplastic*
Squalamine	*Antineoplastic*
Tacedinaline	*Antineoplastic*
Telbivudine	*Antiviral*
Tolevamer	*Antidiarrheal*

Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official *United States Pharmacopeia* or *National Formulary.* A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the *Federal Register* of February 1988.

> All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.

A formal procedure[1] is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all USANs for substances also named by the INN Committee are systematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.

A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.

Submissions to the USAN Council are expected to conform to the established Guiding Principles[2] and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable *category*, are separated by double spacing from the name(s) and *category* for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Suggested USAN	Category
Abatapcept Alfa	*Treatment of autoimmune diseases*
Abatapcim Alfa	
Abatapcimus Alfa	
Abatapfusim Alfa	
Signatapcim Alfa	
Signatapcimus Alfa	
Abtumumab	*Antineoplastic*
Aclatumumab	
Atumumab	
Hutumumab	
Paritumumab	
Ulatumumab	
Aclofarabine	*Treatment of primary refractory or relapsed acute myelogenouse leukemia (AML) or acute lymphoblastic leukemia (ALL)*
Baltarabine	
Clofarabine	
Colfarabine	
Crofarabine	
Eclofarabine	
Iclofarabine	
Adv-2,5-huE1B-deleted-2	*Antineoplastic*
Adv-2,5-hup53-2	
Ixadusugene (E1B deleted)	
Ixadusugene (p53)	
Lontucirev (Replicating Adenovirus)	
Padtucirev (Replicating Adenovirus)	
Agaglitacor	*Antidiabetic; antidyslipidemic*
Atraglitazar	
Onaglitazar	
Optiglitacor	
Sivaglitazar	
Siviglitacor	
Sonaglitacor	
Sonaglitazar	
Sonaglitazet	
Sonaglitazone	
Aglitazar	*Antidiabetic*
Avaglitazar	
Cabaglitazar	
Navaglitazar	
Velaglitazar	

[1] *USP Dictionary of USAN and International Drug Names,* Preface.

[2] Ibid., Appendix VII.

Suggested USAN	Category
Alaglumetad	*Treatment of anxiety and stress disorders*
Eglumetad Alanine	
AHydrochloride	
Xalaglumetad	
Aquifocon A	*Hydrophobic contact lens material*
Aquilafocon A	
Aquilfocon A	
Aquilofocon A	
Arabimodin	*Treatment of type 2 diabetes*
Letaglitazar	
Maraglitazar	
Metabimodin	
Muraglitazar	
Taraglitazar	
Areformoterol Tartrate	*Anti-asthmatic and bronchodilator*
Arformoterol Tartrate	
Armodafinil	*Wake promoting agent*
Artagoxoforb	*Antineoplastic*
Bariloxoforb	
Barilubant	
Eitagoxoforb	
Etagoloxan	
Etagolubant	
Etagolukib	
Etalubloxan	
Igolubant	
Tagolubant	
Artofisopam	*Treatment of irritable bowel syndrome and Crohn's disease*
Dextrofisopam	
Atilizumab	*Monoclonal antibody*
Atlizumab	
Nealizumab	
Nelizumab	
Noralizumab	
Tocilizumab	
Avicurium Chloride	*Neuromuscular blocker*
Bantacurium Chloride	
Benecurium Chloride	
Bravacurium Chloride	
Brevicurium Chloride	
Brosacurium Chloride	
Gantacurium Chloride	
Nexicurium Chloride	
Revacurium Chloride	
Vantacurium Chloride	
Velocurium Chloride	
Zelacurium Chloride	
Balacipladib	*Treatment of pain and symptomatic management of arthritis*
Bicladib	
Ecocipladib	
Ecocladib	
Ecopladib	
Eficipladib	
Eicocladib	
Batabulin Sodium	*Antineoplastic*
Benabulin Sodium	
Turabulin Sodium	
Zabulin Sodium	

Suggested USAN	Category
Becorotan Hydrochloride	*Treatment of Alzheimer's disease*
Becorotane Hydrochloride	
Lecorotan Hydrochloride	
Lecorotane Hydrochloride	
Lecozotan Hydrochloride	
Lecozotane Hydrochloride	
Bepisermin	*Antidiabetic*
Cobasermin	
Derasermin	
Mecasermin Infabate	
Obasermin	
Atamcimod Acetate	*Treatment of chemotherapy-induced diarrhea (CID)*
Binamcimod Acetate	
Delamcimod Acetate	
Delamgatide Acetate	
Bisurex	*Contraceptive; anti-infective*
Cebemirex	
Cebemirside	
Cemisurex	
Cetamox	
Pamiceb	
Buntopitant Citrate	*Antiemetic*
Emepitant Citrate	
Galcopitant Citrate	
Lopitant Citrate	
Maropitant Citrate	
Marpitant Citrate	
Muropitant Citrate	
Ripitant Citrate	
Tanopitant Citrate	
Calimumab	*Treatment of inflammatory disorders such as rheumatoid arthritis, uveitis, asthma, and Crohn's disease*
Relimumab	
Rolimumab	
Zolimumab	
Zylimumab	
Capaprovir	*Treatment of Hepatitis C infection*
Cepaprovir	
Cepaprovirate	
Ciclocivirate	
Cicloprovirate	
Ciluprevir	
Ciluprovir	
Cariporide Mesylate	*Reduction of death and nonfatal myocardial infarction in patients undergoing CABG surgery*
Caripormide Mesylate	
Carlizumab Pegol	*Treatment of rheumatoid arthritis and inflammatory bowel disease, and Crohn's disease*
Certolizumab Pegol	
Melizumab Pegol	
Midrolizumab Pegol	
Santulizimab Pegol	
Ciclesonide	*Treatment of asthma as prophylactic therapy in adults and adolescents*
Cixicirfor	*Stem cell mobilization (CXCR4 antagonist)*
Ericixcrant	
Ericixirfor	

Suggested USAN	Category
Criselestat Didelestat Epelestat Epelestatal	*Treatment of bronchopulmonary inflammatory damage, specifically cystic fibrosis*
Dabuzalgron Hydrochloride	*Treatment of stress urinary incontinence*
Dagitrexol Dartrexol Melitrexol Pelitrexol	*Antineoplastic*
Delnostaurin Hydrochloride Dionestaurin Hydrochloride Enzastaurin Hydrochloride Orapistaurin Hydrochloride Pirinostaurin Hydrochloride	*Antineoplastic*
Didenoson Duodenoson Flodenoson Parmodenoson Regadenoson Regodenoson	*Coronary vasodilator for intravenous use as an adjunct, or pharmacologic stress agent, in radionuclide myocardial perfusion imaging in patients unable to exercise adequately*
Eglumetad	*Treatment of anxiety and stress disorders*
Enterointestinotrophin Gluglycatide Tediglucon Teduglutide Tegludutide Trodiglucon	*Treatment of intestinal diseases*
Fexifotel Perzinfotel Veramafotel Veramfotel	*Treatment of neuropathic pain*
Firosentan Mendoentan Nebantan Potassium Nobentan Potassium Pirosentan Poroentan Potassium Porosentan	*Antineoplastic*
Linxotecan Pegcamtecan Peglinxotecan	*Treatment of small cell lung cancer and gastric adenocarcinoma*
Lufiprazan Revamidam Revaprazan Ucipant	*Acid pump antagonist*
Lumiliximab Riliximab Veriliximab	*Treatment of allergic asthma, allergic rhinitis, chronic lymphocytic leukemia*
Metazamulin Prusarimulin Retezamulin Tezapimulin Zapimulin	*Topical antibiotic for secondarily infected traumatic lesions (SITL) and secondarily infected dermatoses (SID) or impetigo*
Miglustat	*Treatment of lipid storage diseases*
Mubritinib Pavritinib Sardatinib	*Antineoplastic*
Naprogecet Nosprogecet Panprogecet Paprogecet Pazprogecet Piprogecet Sanprogecet Sinprogecet Siprogecet Tanaproget Tanprogecet	*Oral contraceptive*
Nazaxaban Razaxaban Hydrochloride Razoxaban Tozoxaban Zanaxaban Zoxaxaban	*Anticoagulant*
Paclitaxel Conglutamex Paclitaxel Poliglumex Paclitaxel Poliglutamex	*Antineoplastic*
Parathormone (human recombinant) Parathyroid Hormone (human recombinant) Parathyrotropin	*Treatment of osteoporosis*
Probucol Hemisuccinate Resibucol Tebucolide	*Antiproliferative; antioxidant*
Rafelagon Rafelreon Ramelreon Ramelteon Tafelgon Tafelreon Torelagon	*Treatment of sleep disorders*
Human Secretin Secretin Secretin (Human) Secretin (Humanized)	*Diagnostic aid, specifically stimulation of pancreatic secretions*
Senofilcon A Zenafilcon A	*Hydrophilic contact lens material*
Solabegron Hydrochloride	*Antidiabetic*
Stabaczumab Stafabaczumab Staphbaczumab Stefibaczumab	*Treatment of Staphylococcus aureus infections*

Suggested USAN	Category
Tiplactinib	*Treatment of fibrinolytic impairment*
Tiplactinin	
Tiplagtinin	
Tiplastinin	
Tiplaxtinin	
Tiplaxtinor	
Trabectedin	*Antineoplastic*
Valmozamide	*Antiepileptic; anticonvulsant*
Valmozomide	
Valrocemide	
Valtrecemide	
Yttrium Y90 Epratuzumab-DOTA	*Radioimmunotherapy (RAIT) for non-Hodgkin's B-cell lymphoma patients*
Yttrium Y90 Epratuzumab Dotetate	
Yttrium Y90 Epratuzumab Dotetran	

Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* ("Proposed International Nonproprietary Names"). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* ("Recommended International Nonproprietary Names"), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable *category*, are separated by double spacing from the name(s) and *category* for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Nomenclature

Suggested INN	Category
Acrilovirine Axiovirine Triptavirine	*HIV1 non-nucleoside reverse transcriptase inhibitor (NNRTI)*
Adaglen Jaocebrin Resazenil Resevinadine	*Cognitive enhancer*
Adecatumumab Epcatumumab	*Monoclonal antibody*
Adorestat Dorestat Ranarestat	*Treatment of diabetic complications by reducing sorbitol accumulation*
Antithrombin Alfa Antithrombin Alfa (human) Antithrombin Alfa (recombinant)	*Anticoagulant*
Arformoterol Tartrate	*Antiasthmatic*
Armodafinil	*Wake promoting agent*
Artofisopam Dextrofisopam	*Treatment of irritable bowel syndrome, Crohn's disease*
Atlizumab Tocilizumab	*Monoclonal antibody*
Batabulin Sodium	*Antineoplastic*
Cariporide Caripormide	*Reduction of death and nonfatal myocardial infarction in patients undergoing CABG surgery*
Celatopurone Emazenil Emitobran Marcerion	*Antianxiety/antidepressant*
Certolizumab Pegol	*Treatment of rheumatoid arthritis and inflammatory bowel disease; Crohn's disease*
Ciclesonide	*Treatment of asthma as prophylactic therapy in adults and adolescents*
Ciluprevir Ciluprovir	*Treatment of Hepatitis C infection*
Clofarabine	*Treatment of primary refractory or relapsed acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL)*
Dablusagon Dabluzagon Dabuzalgron Zoyanagon	*Treatment of urinary incontinence*
Doranidazole	*Hypoxic cell radiosensitizer*
Dorizem Resizem Salizem	*Treatment of systemic hypertension, stable angina, and supraventicular arrhythmias*
Ecocipladib Ecopladib	*Treatment of pain and symptomatic management of arthritis*
Ecteinibin Ecteinoturbein Trabectedin Trantiblectein Turbinectein	*Antineoplastic*
Emglumegad Eglumetad	*Antianxiety; Smoking cessation*
Enzastaurin	*Antineoplastic*
Etagoloxan Etagolukib	*Antineoplastic*

Suggested INN	Category
Etomilast Tiamilast Tietomilast	*Phosphodiesterase IV inhibitor*
Fluorestrelone Fluorestrenol Fluorestrenolone	*Contraceptive*
Lumiliximab	*Treatment of allergic asthma, allergic rhinitis, chronic lymphocytic leukemia*
Maraglitazar Muraglitazar	*Treatment of Type 2 diabetes*
Maropitant	*Antiemetic*
Maropitant Citrate Marpitant Citrate	*Antiemetic*
Melitrexol Pelitrexol	*Antineoplastic*
Miglustat Miglutrastat	*Treatment of lipid storage diseases*
Mubritinib	*Antineoplastic*
Navaglitazar	*Treatment of Type II Diabetes and associated cardiovascular indications*
Nebantan Nobentan	*Antineoplastic*
Obasermin	*Hormone replacement used in the treatment of diabetes*
Paclitaxel Poliglumex Paclitaxel Poliglutamex	*Antineoplastic*
Parathyroid Hormone	*Treatment of osteoporosis*
Ramelreon Ramelteon	*Treatment of sleep disorders*
Razaxaban	*Anticoagulant; antithrombotic inhibitor of coagulant factor Xa*
Revaprazan	*Acid pump antagonist*
Solabegron	β-*3 Adrenergic receptor agonist intended for use as an antidiabetic*
Sonaglitazar Sonaglitazone	*Antidiabetic; Antidyslipidemic*
Tanprogecet Tanproget	*Oral contraceptive*
Technetium (99m Tc) Diglutide Technetium (99m Tc) Glintrotide Technetium (99m Tc) Protreotide	*To visualize venous thromboemboli, particularly pulmonary embolism*
Teduglutide Tegludutide	*Treatment of intestinal diseases*
Tetrastarch	*Therapy and prophylaxis of hypovolemia*
Tiplactinin Tiplastinin	*Treatment of fibrinolytic impairment diseases*

Nomenclature

INDEX

This is a cumulative directory for the content of all issues of *PF* beginning with *PF* 29(1).

[*Note—This index covers Vol. 29 No. 1, pp. 1–355, Vol. 29, No. 2 pp. 357–563, Vol. 29, No. 3 pp. 565–899, Vol. 29, No. 4 pp. 901–1362, Vol. 29, No. 5 pp. 1363–1782*]

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REFERENCE STANDARDS CATALOG

CHROMATOGRAPHIC REAGENTS USED IN *USP–NF* AND *PHARMACOPEIAL FORUM*

This is an update based on the proposals published in this issue of *PF*.

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PHARMACOPEIAL FORUM VOL. 29 NO. 6 NOV.–DEC. 2003

* The *USP–NF* (*USP27–NF22*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

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PHARMACOPEIAL FORUM VOL. 29 NO. 6 NOV.–DEC. 2003

* The *USP–NF* (*USP27–NF22*), the *Supplement* (*Supp*), or the *Interim Revision Announcement* (*IRA*) for which the revision proposal is targeted is shown in parentheses next to each proposed item.

THE JOURNAL OF STANDARDS DEVELOPMENT AND OFFICIAL COMPENDIA REVISION

Please address comments on *PF* content to Executive Secretariat
USP–NF, 12601 Twinbrook Pkwy.
Rockville, MD 20852

Telephone: 1-301-816-8345
Fax: 1-301-816-8373
http://www.usp.org

Pharmacopeial Forum is covered in *Current Contents/Life Sciences* and in the *Science Citation Index (SCI),* in *International Pharmaceutical Abstracts*, and in *Current Awareness in Biological Sciences.*

The United States Pharmacopeial Convention comprises representatives from colleges and national and state organizations of medicine and pharmacy. It publishes the U.S. Pharmacopeia and National Formulary, the legally recognized compendia of standards for drugs and products of other health care technologies. The USP and NF include assays and tests for the determination of strength, quality, and purity and requirements for packaging and labeling.

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Fax: (301) 816-8148.

STANDARDS DEVELOPMENT

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

USP publishes *Pharmacopeial Forum* (*PF*) bimonthly as the working vehicle of the USP Council of Experts. *PF* provides interested parties an opportunity to review and comment as the Council of Experts develops or revises standards for the *United States Pharmacopeia* and the *National Formulary* (*USP–NF*).

PF includes the following:

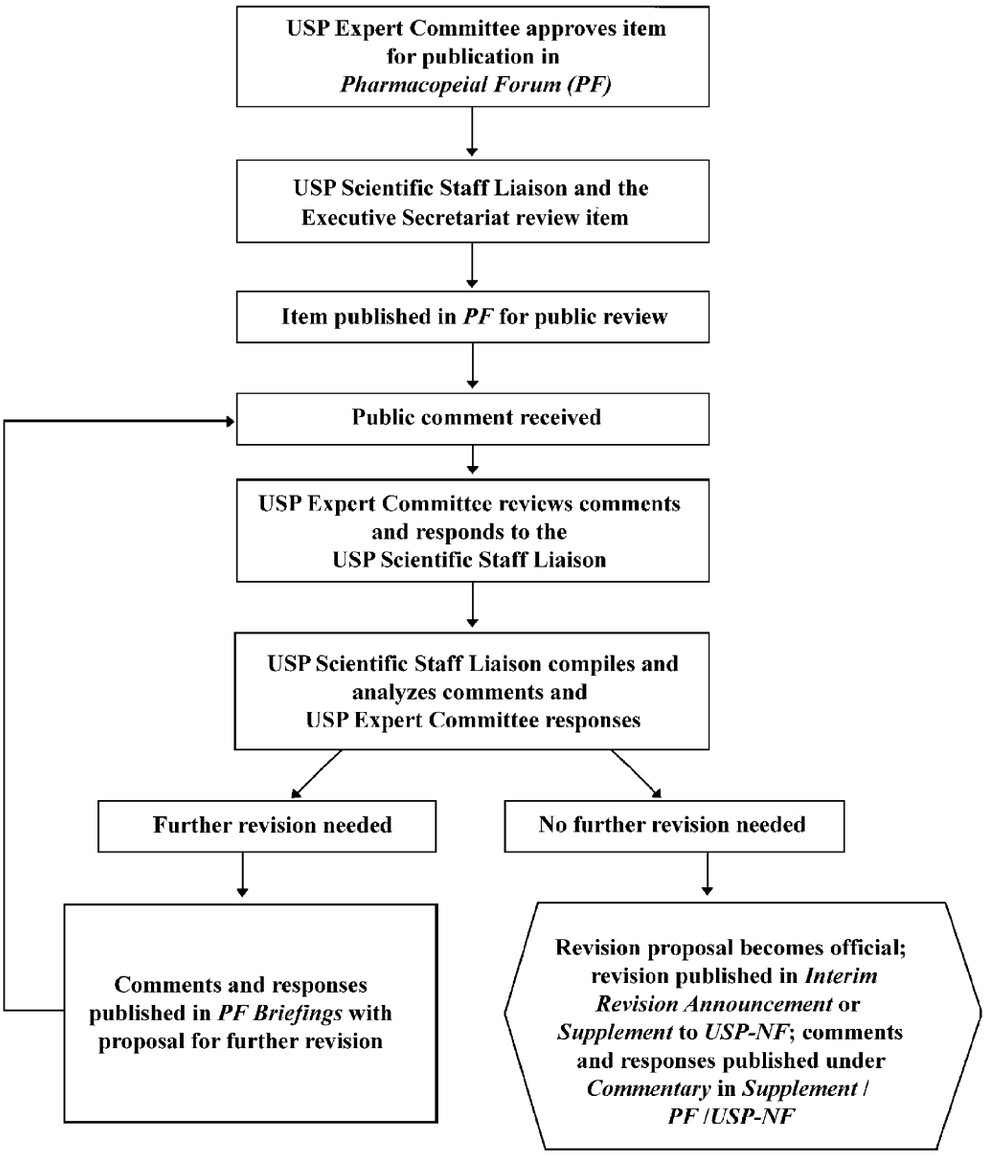
1. Potential revisions—entirely new standards, revision ideas, and drafts not yet targeted for official adoption (*Pharmacopeial Previews*)
2. Proposed revisions—new or revised standards targeted for official adoption (*In-Process Revision*)
3. Adopted revisions—new or revised standards that become official and binding before the publication of the next *USP–NF* or *Supplement* (*Interim Revision Announcement*)

USP welcomes comments and data on potential, proposed, or official standards.* Comments, along with USP's responses, will be published either in *PF Briefings*, the *Commentary* section of *PF*, the *Commentary* section of *Supplements* to *USP–NF*, or the *Commentary* section of *USP–NF*.

* If you are not immediately able to submit comments but you intend to do so, please notify USP by using the Intent to Comment form provided before the section *Chromatographic Reagents Used in USP–NF and PF*.

The chart below shows the public review and comment process and its relationship to standards development.

Public Review and Comment Process for Standards Development



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

HOW TO USE *PF*

This section provides descriptions of the various parts of *PF*. It also includes *Committee Designations* and the *Staff Directory*.

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

Proposed and Adopted Revisions

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

Other Sections

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

Staff Directory
Names of all USP scientific staff liaisons with contact information.

Policies and Announcements
- General scientific and policy issues affecting *USP–NF* standards and processes
- Update on standards-related issues being considered by USP
- Summaries of meetings of the Council of Experts
- Guidelines on how to comment
- Publication and comment schedules

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

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

Index
Cumulative directory for the content of all issues of *PF* beginning with *PF* 29(1).

Reference Standards Catalog
List of official USP Reference Standards specified in *USP–NF*, along with availability and ordering information.

Chromatographic Reagents Used in USP–NF* and *Pharmacopeial Forum
Update of chromatographic reagents based on the proposals published in this issue of *PF*.

EXPERT COMMITTEE DESIGNATIONS*

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

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

* **HDQ** Indicates USP Headquarters items.
† The Expert Committee has been renamed. The old name, Excipients—Substances and Characterization (ESC) has been changed to Excipient Monograph Content (EMC).

STAFF DIRECTORY

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

STAFF	E-MAIL	PHONE	ASSIGNMENT
Clydewyn M. Anthony, Senior Scientific Associate	cma@usp.org	(301) 816-8139	Pharmaceutical Analysis 1 (PA1)
Frank P. Barletta, Consultant	fpb@usp.org	(301) 816-8328	Pharmaceutical Waters (PW)
Charles H. Barnstein, Consultant	chbarnstein@email.msn.com	(301) 774-9457	Nomenclature and Labeling (NL)
Daniel K. Bempong, Scientist	dkb@usp.org	(301) 816-8143	Excipient Monograph Content (EMC)
Lokesh Bhattacharyya, Director, Non-Complex Actives and Excipients	lb@usp.org	(301) 816-8201	
Barbara A. Bowman, Manager, Administrative Services	bab@usp.org	(301) 816-8278	USP Correspondence
William E. Brown, Scientist	web@usp.org	(301) 816-8380	Biopharmaceutics (BPC); Biostatistics (BST)
Evelyn Bryant, Manager, Editorial Services	eb@usp.org	(301) 816-8302	
Todd L. Cecil, Director, General Policies and Requirements	tlc@usp.org	(301) 816-8234	
Roger Dabbah, Director, Complex Actives	rd@usp.org	(301) 816-8336	
Behnam Davani, Scientist	bd@usp.org	(301) 816-8394	Pharmaceutical Analysis 7—Antimicrobial and Antivirals (PA7b)
Ian F. DeVeau, Senior Scientist	ifd@usp.org	(301) 816-8178	Cell Therapy, Gene Therapy and Tissue Engineering (CGT); Veterinary Products and Natural Products Monographs
Lawrence Evans, Senior Scientific Associate	le@usp.org	(301) 816-8389	Pharmaceutical Analysis 6 (PA6); Dietary Supplements—Non-Botanicals (DSN)
L. Valentin Feyns, Director, Reference Standards Evaluation	lvf@usp.org	(301) 816-8121	USP Reference Standards
John W. Gasper, Director, Executive Secretariat	jg@usp.org	(301) 816-8241	General Issues
Gabriel I. Giancaspro, Senior Scientist and Latin American Liaison	gig@usp.org	(301) 816-8343	Dietary Supplements—Botanicals (DSB); Dietary Supplements—Bioavailability and Nutrient Absorption (BNA)

STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
Elena Gonikberg, Scientist	eg@usp.org	(301) 816-8251	Pharmaceutical Analysis 4 (PA4)
James W. Kelly, Scientist	jwk@usp.org	(301) 816-8167	Pharmaceutical Analysis 2 (PA2); Parenteral Products—Industrial (PPI)
Justin J. Lane, Senior Scientific Associate	jl@usp.org	(301) 816-8323	Excipients—Test Methods (ETM)
Anju K. Malhotra, Manager, Conferences and Meetings	akm@usp.org	(301) 816-8346	USP Conferences and Meetings
Ronald G. Manning, Vice President, Standards Operations	rgm@usp.org	(301) 816-8562	
Margareth R. Marques, Scientist and Latin American Liaison	mrm@usp.org	(301) 816-8106	Biopharmaceutics (BPC); Reagents
Alan W. Nichols, Director, Reference Standards Production	awn@usp.org	(301) 816-8321	USP Reference Standards
Claudia C. Okeke, Associate Director	cco@usp.org	(301) 816-8243	Compounding Pharmacy (CRX); Parenteral Products—Compounding and Preparation (PPC); Packaging, Storage, and Distribution (PSD)
W. Larry Paul, Scientific Fellow	wlp@usp.org	(301) 816-8331	Nomenclature and Labeling (NL); Pharmaceutical Dosage Forms (PDF)
Horacio Pappa, Scientist and Latin American Liaison	hp@usp.org	(301) 816-8319	Pharmaceutical Dosage Forms (PDF)
David A. Porter, Associate Director	dap@usp.org	(301) 816-8225	Analytical Microbiology (AMB); Biotechnology and Natural Therapeutics and Diagnostics (BNT); General Toxicity and Biocompatibility (GTB)
Gary E. Ritchie, Scientific Fellow for PAT	ger@usp.org	(301) 816-8353	Process Analytical Technology (PAT)
David B. Roll, Director, Dietary Supplements	dbr@usp.org	(301) 816-8316	
Karen A. Russo, Scientist	kar@usp.org	(301) 816-8379	Pharmaceutical Analysis 1 (PA1); Excipient New Monograph Development
Jennifer Salguero, Scientist	jxs@usp.org	(301) 816-8371	Dietary Supplement Information
Salvador Salado, Scientist and Latin American Liaison	ss@usp.org	(301) 816-8165	Pharmaceutical Analysis 3 (PA3)
Stefan P. Schuber, Director, Information and Administration	sps@usp.org	(301) 816-8551	
Catherine M. Sheehan, Senior Scientific Associate	cxs@usp.org	(301) 816-8262	Excipient Monograph Content (EMC)
Eric B. Sheinin, Vice President, Information and Standards Development	es@usp.org	(301) 816-8103	
Radhakrishna S. Tirumalai, Scientist	rst@usp.org	(301) 816-8339	Blood and Blood Products (BBP); Vaccines, Virology, and Immunology (VVI)

STAFF DIRECTORY *(continued)*

STAFF	E-MAIL	PHONE	ASSIGNMENT
Andrzej Wilk, Senior Scientific Associate	aw@usp.org	(301) 816-8305	Pharmaceutical Analysis 5 (PA5); Radiopharmaceuticals and Medical Imaging (RMI)
William W. Wright, Scientific Fellow	www@usp.org	(301) 816-8335	Pharmaceutical Analysis 7—Antibiotics (PA7a)
Kahkashan Zaidi, Scientist	kxz@usp.org	(301) 816-8269	Aerosols (AER)

POLICIES AND ANNOUNCEMENTS

In this section, readers may find statements about general scientific and policy issues that may have an impact on *USP–NF* standards and processes, announcements about issues being considered by USP, and summaries of Council of Experts meetings. This section also includes publication and comment schedules.

NEW DIRECTOR NAMED FOR NON-COMPLEX ACTIVES AND EXCIPIENTS.
USP is pleased to announce that Lokesh Bhattacharyya, Ph.D., has been named as the new Director, ISD for Non-Complex Actives and Excipients. As part of his duties, he will be responsible for the development of monographs and general chapters for non-complex drug substances and products as well as excipients. In addition, he will also be involved in the PDG efforts toward harmonization.

Most recently, Dr. Bhattacharyya was the USP Senior Scientist responsible for the Blood and Blood Products Expert Committee as well as the Vaccines, Virology, and Immunology Expert Committee. Prior to joining USP, he gained significant industrial experience in the pharmaceutical and biotechnology research and development arena.

Dr. Bhattacharyya may be reached by telephone at 301-816-8201, and his email address is lb@usp.org.

USP CONFERENCE ON BIOLOGICAL AND BIOTECHNOLOGICAL DRUG SUBSTANCES AND PRODUCTS, NOVEMBER 19–21, 2003.

This conference will be held in the Marriot Crystal City Gateway in Crystal City, Virginia. It is intended for those responsible for the development and maintenance of quality standards in this field. There are several objectives for this meeting:

- To involve industry and regulatory agencies in the development of quality standards for these products
- To promote the utility of standards for these products as necessary from regulatory and quality perspectives
- To involve stakeholders in the development of the future USP blueprint in these areas
- To promote the utility of USP as a neutral body bridging industry and the regulatory agencies for the benefit of public health.

This conference will consist of formal presentations and workshops led by nationally and internationally recognized experts in different areas of interest to the biological and biotechnological industry. Conference topics will include the following:

- Equivalence of biological and biotechnological drug substances and products
- Biotechnology-derived products
- Blood-derived products
- Vaccines
- Cell and gene therapy, and tissue engineering
- Bioassay
- Ancillary products.

For program information, contact Lokesh Bhattacharyya at 301-816-8201 or lb@usp.org. For conference registration information, call 301-816-8226, or register online at www.usp.org/conferences.

USP GUIDELINE FOR SUBMITTING REQUESTS FOR REVISION TO THE *USP–NF.* We are pleased to announce the availability of the *USP Guideline for Submitting Requests for Revision to the USP–NF*. This document was developed in conjunction with the USP Council of Experts and its Expert Committees, USP Staff, and the Drug Substance, Complex Actives, and Excipients Project Teams of the Prescription/Nonprescription Stakeholders Forum. This document includes information to aid submission of new monographs and revisions to existing monographs for Non-Complex Active Substances and Products, Biological and Biotech Substances and Products, Excipients, and Vaccines. It incorporates many of the concepts and suggestions included in the ICH Q3A, Q3B, Q3C, Q6A, and Q6B guidelines. These include the definition of a specification and incorporate much of the terminology of Q3A for the control of impurities. The guideline clearly defines the information needed for the USP's Council of Experts and its Expert Committees to evaluate a request for revision. The document is approximately 75 pages in length with about 25 pages of addenda and is available in PDF format from the USP website at www.usp.org. Hard copies will be provided upon request.

PHARMACOPEIAL EDUCATION COURSES. USP's Pharmacopeial Education series has been developed to enhance the knowledge, skills, and expertise of pharmaceutical industry personnel.

The following list indicates tentatively scheduled course dates. For further information, contact Barbara B. Hubert, Director, Pharmacopeial Education, BBH@usp.org, 301-816-8333, or Diana Lenahan, Program Associate, DPL@usp.org, 301-816-8530.

Calendar of Pharmacopeial Education Courses, 2003

Date	Name of course	Location
November 17 and 18	Fundamentals of Dissolution	USP Headquarters, Rockville, MD
December 8	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 9	Standards 101: Advanced Use of *USP–NF*, General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
December 15 and 16	Fundamentals of Dissolution	USP Headquarters, Rockville, MD

Calendar of Pharmacopeial Education Courses, 2004

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

Calendar of Pharmacopeial Education Courses, 2004 (*continued*)

Date	Name of course	Location
November 12	Standards 101: Advanced Use of *USP–NF*, General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD
November 12	Fundamentals of Dissolution (Lecture)	USP Headquarters, Rockville, MD
December 2	Analytical Method Validation	USP Headquarters, Rockville, MD
December 8	Standards 100: Fundamentals of the Use of *USP–NF* and the Standards Development Process	USP Headquarters, Rockville, MD
December 9	Standards 101: Advanced Use of *USP–NF*, General Notices, and Monograph Chapters	USP Headquarters, Rockville, MD

Call 301-816-8530 to get information on customized courses offered at USP or at your site.

VISIT THE USP WEB SITE AT ⟨http://www.usp.org⟩. Various resources related to Pharmacopeial standards are presented, including highlights from *PF*.

***USP–NF* AVAILABLE IN THREE ELECTRONIC FORMATS.** The trusted reference for official pharmaceutical standards is available in three convenient electronic formats—CD, intranet, and online. The CD is ideal for single users who prefer to have *USP–NF* on their hard drives. The intranet format allows Web browser-based access to multiple users within a company, through their own intranet server. The online format can be accessed by individual registered users through the World Wide Web. All three electronic formats provide fast and easy access to official *USP–NF* content. More information can be obtained by visiting www.usp.org/products or by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

***CHROMATOGRAPHIC REAGENTS* NOW AVAILABLE.** *Chromatographic Reagents* lists the brand names of the column reagents cited in every proposal for new or revised gas- or liquid-chromatographic test methods that has been published in *Pharmacopeial Forum* (*PF*) since 1980. *Chromatographic Reagents* also helps to track which column reagents were used to validate methods that have become official and are included in *USP–NF*. The branded column reagents list is updated bimonthly through *Pharmacopeial Forum*. *Chromatographic Reagents* can be ordered by calling USP's Customer Service Department at 1-800-227-8772 or 301-881-0666.

INTERNATIONAL CORRESPONDENCE. Individuals who wish to correspond with the European and Japanese Pharmacopoeias concerning monographs in the Official Inquiry and Consensus stages of international harmonization should address their comments to the coordinating pharmacopeia for a given article. The addresses for the European and Japanese Pharmacopoeias are as follows:

Technical Secretariat of the
European Pharmacopoeia Commission
B.P. 907
F 67029 Strasbourg Cedex 1
France

NAKASHIMA Nobumasa
Evaluation and Licensing Division
Pharmaceutical and Medical Safety Bureau
Ministry of Health, Labour and Welfare, Japan
Tel. +81-3-3595-2431, Fax. +81-3-3597-9535
E-mail: nakashima-nobumasa@mhlw.go.jp

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

Please note that *USP–NF* is being published in an annual edition with one main book and two Supplements a year. In addition, the following schedule will repeat every year so that users will know what to expect and become familiar with the deadlines.

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

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

The publication and comment schedule for *USP 28–NF 23* is as follows:

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

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

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

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

PUBLICATION SCHEDULES

Publication	Publication Date	Official Date
1st Supplement	Feb. 2003	Apr. 1, 2003
PF 29(2) [Mar.–Apr. 2003]	Mar. 2003	Not Applicable
2nd IRA [published in *PF* 29(2)]	Mar. 2003	Apr. 1, 2003
PF 29(3) [May–June 2003]	May 2003	Not Applicable
3rd IRA [published in *PF* 29(3)]	May 2003	June 1, 2003
2nd Supplement	June 2003	Aug. 1, 2003
PF 29(4) [July–Aug. 2003]	July 2003	Not Applicable
4th IRA [published in *PF* 29(4)]	July 2003	Aug. 1, 2003
PF 29(5) [Sept.–Oct. 2003]	Sept. 2003	Not Applicable
5th IRA [published in *PF* 29(5)]	Sept. 2003	Oct. 1, 2003
PF 29(6) [Nov.–Dec. 2003]	Nov. 2003	Not Applicable
6th IRA [published in *PF* 29(6)]	Nov. 2003	Dec. 1, 2003

INTERIM REVISION ANNOUNCEMENT

In this section readers will find the following:

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

Readers should review this section to determine if they are affected by any of the changes.

Symbols—Interim revisions are shown with new text (if any) enclosed in circles, •new text•. Text enclosed in squares, ▪new text▪, has already been adopted in a *Supplement*. Where the symbols appear together with no enclosed text, such as •• or ▪▪, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by a number that indicates the *IRA* or *Supplement* in which the revision first appeared. For example, •2 indicates that the revision was officially adopted in the *Second Interim Revision Announcement*, and ▪2S (*USP 26*) indicates that the revision was officially adopted in the *Second Supplement* to *USP 26*.

Errata—At the end of the *Interim Revision Announcement* section is a list of errata and corrections to *USP 26–NF 21*. The page number indicates where the item is found in *USP–NF*. If necessary, this list will be updated with every issue of *PF*. This information will also be cumulative in the next available *Supplement*, and will appear in its corrected form in the next annual edition of *USP–NF*. Errata are considered to be items erroneously published that have not received the approval of the Council of Experts and that do not reflect the official requirement.

SIXTH INTERIM REVISION ANNOUNCEMENT to *USP 26* and to *NF 21*

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

Larry L. Braden, *Chair*
USP Board of Trustees

Roger L. Williams, *Executive Vice President*
and *Chairman, USP Council of Experts*

John W. Gasper, *Director*, *Executive Secretariat*

Official December 1, 2003. **Released November 3, 2003.**

All inquiries and comments regarding *USP 26* text and *NF 21* text should be addressed to the Executive Secretariat, *USP–NF*, 12601 Twinbrook Parkway, Rockville, MD 20852.

New USP Reference Standards

The following USP Reference Standards, which were indicated in past *Supplements to USP–NF* as being not yet available, have since become available. Thus, the official date of each *USP 26* or *NF 21* standard, test, or assay requiring the use of the following Reference Standards is indicated individually in this list.

USP Acesulfame Potassium RS (January 1, 2004)
USP Alendronate Sodium RS (November 1, 2003)
USP Allantoin RS (March 1, 2004)
USP Amifostine Disulfide RS (March 1, 2004)
USP Amitraz RS (November 1, 2003)
USP Ammonium Chloride RS (March 1, 2004)
USP Aspartame Acesulfame RS (March 1, 2004)
USP Benazepril Related Compound A RS (May 1, 2004)
USP Benazepril Related Compound B RS (May 1, 2004)
USP Betahistine Hydrochloride RS (January 1, 2004)
USP Brinzolamide RS (November 1, 2003)
USP Brinzolamide Related Compound A RS (November 1, 2003)
USP Brinzolamide Related Compound B RS (November 1, 2003)
USP Bupropion Hydrochloride RS (March 1, 2004)
USP Cefipime Hydrochloride RS (January 1, 2004)
USP Cefipime Hydrochloride System Suitability RS (January 1, 2004)
USP Cetyl Palmitate RS (November 1, 2003)
USP Choline Bitartrate RS (January 1, 2004)
USP Choline Chloride RS (March 1, 2004)
USP Clozapine RS (November 1, 2003)
USP Copovidone RS (March 1, 2004)
USP Desflurane RS (May 1, 2004)
USP Desflurane Related Compound A RS (March 1, 2004)
USP Dextran 40 RS (May 1, 2004)
USP Dextran 70 RS (May 1, 2004)
USP Dextran 4 Calibration RS (November 1, 2003)
USP Dextran 10 Calibration RS (November 1, 2003)
USP Dextran 40 Calibration RS (November 1, 2003)
USP Dextran 70 Calibration RS (November 1, 2003)
USP Dextran 250 Calibration RS (November 1, 2003)
USP Diloxanide Furoate RS (November 1, 2003)
USP Dinoprostone RS (November 1, 2003)
USP Dorzolamide RS (November 1, 2003)
USP Dorzolamide Hydrochloride Related Compound A RS (January 1, 2004)
USP Doxazosin Mesylate RS (March 1, 2004)
USP Emedastine Difumarate RS (November 1, 2003)
USP Ethinyl Estradiol Related Compound A RS (November 1, 2003)
USP Fenoldopam Mesylate RS (March 1, 2004)
USP Fenoldopam Related Compound A RS (January 1, 2004)
USP Fenoldopam Related Compound B RS (January 1, 2004)
USP Flumazenil RS (May 1, 2004)
USP Formononetin RS (March 1, 2004)
USP Fosphenytoin Sodium RS (March 1, 2004)
USP Gadoversetamide RS (March 1, 2004)
USP Gadoversetamide Related Compound A RS (March 1, 2004)
USP Ganciclovir RS (May 1, 2004)
USP Gemfibrozil Related Compound A RS (January 1, 2004)
USP Glutamic Acid RS (November 1, 2003)
USP Glycyrrhizic Acid RS (November 1, 2003)
USP Hydrocodone Bitartrate Related Compound A CII RS (March 1, 2004)
USP Isoflupredone Acetate RS (January 1, 2004)
USP Powdered Kava Extract RS (March 1, 2004)
USP Kawain RS (March 1, 2004)
USP Ketamine Related Compound A RS (January 1, 2004)
USP Lansoprazole RS (November 1, 2003)
USP Lansoprazole Related Compound A RS (November 1, 2003)
USP Meropenem RS (March 1, 2004)
USP Metformin Hydrochloride RS (March 1, 2004)
USP Metformin Related Compound A RS (March 1, 2004)
USP Powdered Milk Thistle Extract RS (November 1, 2003)
USP Milrinone RS (November 1, 2003)
USP Milrinone Related Compound A RS (November 1, 2003)
USP Nabumetone RS (January 1, 2004)
USP Norgestimate RS (January 1, 2004)
USP Ondansetron Hydrochloride RS (March 1, 2004)
USP Ondansetron Related Compound A RS (March 1, 2004)
USP Ondansetron Related Compound C RS (March 1, 2004)
USP Ondansetron Related Compound D RS (March 1, 2004)
USP Oxaprozin RS (January 1, 2004)
USP Oxfendazole RS (March 1, 2004)
USP Paclitaxel RS (March 1, 2004)
USP Paclitaxel Related Compound A RS (March 1, 2004)
USP Paclitaxel Related Compound B RS (March 1, 2004)
USP Paroxetine Related Compound D RS (May 1, 2004)
USP Phenytoin Related Compound A RS (March 1, 2004)
USP Poloxalene RS (November 1, 2003)
USP Quinapril Related Compound A RS (January 1, 2004)
USP Quinapril Related Compound B RS (January 1, 2004)
USP Quinine Hydrochloride Dihydrate RS (March 1, 2004)
USP Ramipril RS (January 1, 2004)
USP Ramipril Related Compound A RS (January 1, 2004)
USP Powdered Red Clover Extract RS (May 1, 2004)
USP Sevoflurane RS (May 1, 2004)
USP Sevoflurane Related Compound A RS (May 1, 2004)
USP Sodium Starch Glycolate RS (January 1, 2004)
USP Sotalol Related Compound A RS (May 1, 2004)
USP Sotalol Related Compound B RS (May 1, 2004)
USP Sotalol Related Compound C RS (May 1, 2004)
USP Stearoyl Polyoxyglycerides RS (May 1, 2004)
USP Sumatriptan RS (March 1, 2004)
USP Sumatriptan Succinate RS (March 1, 2004)
USP Sumatriptan Succinate Related Compound A RS (March 1, 2004)
USP Sumatriptan Succinate Related Compound C RS (March 1, 2004)
USP Tacrine Hydrochloride RS (January 1, 2004)
USP Taurine RS (January 1, 2004)
USP Terazosin Hydrochloride RS (March 1, 2004)
USP Terazosin Related Compound A RS (March 1, 2004)
USP Terazosin Related Compound B RS (March 1, 2004)
USP Terazosin Related Compound C RS (March 1, 2004)
USP Tiletamine Hydrochloride RS (November 1, 2003)
USP Tinidazole RS (January 1, 2004)
USP Tinidazole Related Compound A RS (January 1, 2004)
USP Thalidomide RS (January 1, 2004)
USP Tylosin RS (November 1, 2003)
USP Urea C13 RS (January 1, 2004)
USP Valsartan Related Compound A RS (March 1, 2004)
USP Valsartan Related Compound C RS (March 1, 2004)
USP Verteporfin RS (March 1, 2004)
USP Verteporfin Related Compound A RS (March 1, 2004)
USP Vinorelbin Related Compound A RS (March 1, 2004)
USP Vinorelbine Tartrate RS (May 1, 2004)
USP Vitexin RS (March 1, 2004)
USP Zileuton RS (January 1, 2004)
USP Zileuton Related Compound A RS (November 1, 2003)
USP Zileuton Related Compound B RS (November 1, 2003)
USP Zileuton Related Compound C RS (November 1, 2003)

The official dates of any *USP 26* or *NF 21* standards, tests, or assays requiring the use of the following new USP Reference Standards are postponed until further notice pending availability of the respective Reference Standards.

USP Alteplase RS
USP Amiloxate RS
USP Positive Bioreaction RS
USP Cefpiramide RS
USP Cinoxate RS
USP Clonazepam Related Compound C RS
USP Decoquinate RS
USP Diethylstilbestrol Diphosphate RS
USP Enalapril Related Compound B RS
USP Enzacamene RS
USP Fludeoxyglucose RS
USP Ginseng Extract RS
USP Gonadorelin Hydrochloride RS
USP Hypericin RS
USP Lactase RS
USP Medroxyprogesterone Acetate Related Compound A RS
USP Menotropins RS
USP Methyldopa–Glucose Reaction Product RS
USP Mibolerone RS
USP Narasin RS
USP Ondansetron Related Compound B RS
USP Potassium Perchlorate RS
USP Pyrethrum Extract RS
USP Sargramostim RS
USP Sulisobenzone RS
USP Δ^8-tetrahydrocannabinol RS
USP Δ^9-tetrahydrocannabinol RS
USP Thiacetarsamide RS
USP Tilmicosin RS
USP Tinidazole Related Compound B RS
USP Trenbolone RS
USP Trenbolone Acetate RS
USP Powdered Valerian RS
USP Vasopressin RS

USP 26 MONOGRAPHS

Cefuroxime Axetil Tablets

Change to read:

Labeling—The labeling indicates whether the Tablets contain amorphous or crystalline Cefuroxime Axetil. If Tablets contain a mixture of amorphous and crystalline Cefuroxime Axetil, label to indicate the percentage of each contained therein. •When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.•6

Change to read:

Dissolution ⟨711⟩—

•TEST 1—•6

Medium: 0.07 N hydrochloric acid; 900 mL.

Apparatus 2: 55 rpm.

Times: 15 and 45 minutes.

Procedure—Determine the amount of cefuroxime ($C_{16}H_{16}N_4O_8S$) dissolved by employing UV absorption at the wavelength of maximum absorbance at about 278 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Cefuroxime Axetil RS, equivalent to about 0.01 to 0.02 mg of cefuroxime ($C_{16}H_{16}N_4O_8S$) per mL, in the same *Medium.*

Tolerances—Not less than 60% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 15 minutes, and not less than 75% (*Q*) is dissolved in 45 minutes; except that where Tablets are labeled to contain the equivalent of 500 mg of cefuroxime, not less than 50% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 15 minutes, and not less than 70% (*Q*) is dissolved in 45 minutes.

•TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Apparatus 2: 100 rpm.

Medium, Times, and *Procedure*—Proceed as directed under *Test 1.*

Tolerances—Not less than 60% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 15 minutes, and not less than 75% (*Q*) of the labeled amount of $C_{16}H_{16}N_4O_8S$ is dissolved in 45 minutes.•6

Ciclopirox Olamine Cream

Change to read:

Identification—••6Dilute 4 mL of the *Assay preparation* obtained as directed in the *Assay* with a mixture of methanol and 6.25 N sodium hydroxide (123:2) to make 100 mL: the UV absorption spectrum of the solution so obtained exhibits maxima and minima at the same wavelengths as that of a similar solution prepared from the *Standard preparation* obtained as directed in the *Assay*, concomitantly measured.

••6

Pseudoephedrine Hydrochloride Extended-Release Tablets

Add the following:

•**Labeling—**When more than one *Drug Release* test is given, the labeling states the *Drug Release* test used only if *Test 1* is not used.•6

Add the following:

•**Drug release** ⟨724⟩—

FOR PRODUCTS LABELED FOR DOSING EVERY 12 HOURS—

TEST 1—

Medium: water; 900 mL.

Apparatus 2: 50 rpm

Times: 1, 3, and 6 hours.

Standard solution—Dissolve an accurately weighed quantity of USP Pseudoephedrine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.13 mg per mL.

Procedure—Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved by employing the procedure set forth in the *Assay*. Separately inject equal volumes (about 50 µL) of the *Standard solution* and the filtered solution under test. Calculate the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved per Tablet.

Times and Tolerances:

Time (hours)	Amount dissolved
1	between 25% and 45%
3	between 50% and 75%
6	not less than 75%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3.*

Medium, Apparatus, and *Times*—Proceed as directed for *Test 1.*

Procedure—Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 214 nm on portions of the solution under test, filtered through a 0.45-µm filter and suitably diluted with *Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Pseudoephedrine Hydrochloride RS in the same *Medium*.

Times and Tolerances:

Time (hours)	Amount dissolved
1	between 25% and 45%
3	between 60% and 80%
6	not less than 80%

FOR PRODUCTS LABELED FOR DOSING EVERY 24 HOURS—

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Medium: 0.9% sodium chloride in water; 50 mL.

Apparatus 7: 30 cycles per minute; 2–3 cm amplitude. To prepare the sample, see Figure 1 below that illustrates the following steps:

1. Place one Tablet on a 5- × 5-cm nylon netting.
2. Fold netting over the Tablet. Continue folding until the Tablet is enclosed in netting.
3. Fold netting so that the two open ends meet. The Tablet should be enveloped in the center of the netting.
4. Insert rod (see *Figure 7c* under *Drug Release* ⟨724⟩) through netting to secure the Tablet.
5. Secure netting with HPLC plastic ferrules or other appropriate device. Trim the excess netting. Attach each sample holder to the vertically reciprocating sample holder.

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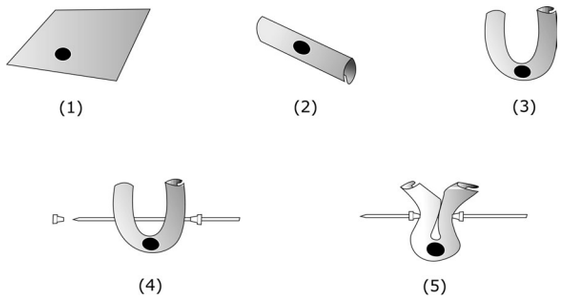

Fig. 1

Times: 2, 8, 14, and 24 hours.

Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved by employing the following method.

0.05 M Phosphate buffer, pH 6.8—Transfer 200 mL of water to a 1000-mL volumetric flask. Add 3.4 mL of phosphoric acid and 5 mL of triethylamine. Add water to almost 900 mL. Adjust with 1 N sodium hydroxide to a pH of about 6.8, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *0.05 M Phosphate buffer, pH 6.8* and methanol (9:1).

System suitability solution—Dissolve an accurately weighed quantity of USP Pseudoephedrine RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.4 mg per mL.

Standard solutions—Prepare solutions in water having accurately known concentrations of USP Pseudoephedrine Hydrochloride RS in a range around the expected concentration of the solution under test at each time interval.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 5-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the tailing factor for the analyte peak is not more than 2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solutions* and the solution under test into the chromatograph, record the chromatograms, and measure the responses for the major peak. Construct a calibration curve by plotting the peak response versus concentration of the *Standard solutions*. Determine the amount of $C_{10}H_{15}NO \cdot HCl$ dissolved at each time interval from a linear regression analysis of the calibration curve.

Times and Tolerances:

Time (hours)	Amount dissolved
2	between 20% and 35%
8	between 40% and 65%
14	between 60% and 90%
24	not less than 85% ●6

GENERAL CHAPTERS

General Tests and Assays

⟨11⟩ USP REFERENCE STANDARDS

Change to read:

USP 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril RS—●(NAME CHANGE) See *USP Diazepam Related Compound B RS*.●6

Change to read:

USP 2-*tert*-Butyl-4-hydroxyanisole RS ($C_{11}H_{16}O_2$ ✧ 180.25)—Do not dry before using. Keep container tightly closed. ●Store in a cool place. Protect from light.●6

Change to read:

USP Carboplatin RS—●Do not dry. Keep container tightly closed. Protect from light. Store in a refrigerator.●6

Change to read:

USP Clavam-2-Carboxylate Potassium RS—▲▲2S (*USP26*)●Each vial contains 3 µg of clavam-2-carboxylate potassium dispersed in poly(vinylpyrrolidone). For quantitative applications, reconstitute the entire contents with a suitable volume of water. Do not dry. Keep container tightly closed. Protect from light. Store in a freezer.●6■*Standard solutions* may be stored in a refrigerator for 1 week.■2S (*USP26*)

Change to read:

USP Clotrimazole RS—●Do not dry. Keep container tightly closed. Protect from light.●6

Add the following:

●**USP Diazepam Related Compound B RS**—($C_{16}H_{13}ClN_2O$ ✧ 284.74)—Do not dry. Keep container tightly closed. Protect from light.●6

Change to read:

USP Dihydrocapsaicin RS—●Do not dry. Keep container tightly closed. Protect from light.●6

Change to read:

USP Dolasetron Mesylate RS—●This is the monohydrate form of dolasetron mesylate. Do not dry. Keep container tightly closed.●6

Change to read:

USP Dolasetron Mesylate Related Compound A RS ●[Hexahydro-8-hydroxy-2,6-methano-2*H*-quinolizin-3 (4*H*)-one, hydrochloride]—Do not dry. Keep container tightly closed.●6

Change to read:

USP Powdered Eleuthero Extract RS—●Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Store in a refrigerator. This material is hygroscopic.●6

Change to read:

USP Flumazenil RS—●Do not dry. Keep container tightly closed. Protect from light.●6

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Change to read:

■**USP Ganciclovir RS**■1S (*USP26*)—•Store in a refrigerator. This material is hygroscopic.•6

Change to read:

USP Ioxilan RS—•Do not dry. For quantitative applications, determine the water content titrimetrically at the time of use. Keep container tightly closed. Protect from light.•6

Change to read:

USP Ketoconazole RS—•Do not dry before use. Keep container tightly closed.•6

Change to read:

USP Lovastatin Related Compound A RS •**[**dihydro-lovastatin**]**•6 **[**butanoic acid, 2-methyl-, 1,2,3,4,4a,7,8,8a-octahydro-3,7-dimethyl-8-[2(tetrahydro-4-hydroxy-6-oxo-2*H*-pyran-2-yl)-ethyl]-1-naphthalenyl ester, [1*S*-[1α(R*),3α,7β,8β(2S*,4S*),-8αβ]]-**]** ($C_{24}H_{38}O_5$ ✧ 406.56)—Do not dry. •This material is hygroscopic. Keep container tightly closed. Protect from light. Store in a refrigerator.•3

Change to read:

USP Mesoridazine Besylate RS—•Do not dry. Keep container tightly closed. Protect from light.•6

Change to read:

USP Mestranol RS—•Do not dry. Keep container tightly closed. Protect from light.•6

Change to read:

USP Methylprednisolone Hemisuccinate RS—•Do not dry. Keep container tightly closed. Protect from light. Store in a cool place.•6

Add the following:

•**USP Nitrofurazone Related Compound A RS [**5-Nitro-2-fufuraldazine**]** ($C_{10}H_6N_4O_6$ ✧ 278.18)—Dry portion at 105° for 1 hour before using. Keep container tightly closed. Protect from light.•6

Change to read:

USP 5-Nitro-2-furfuraldazine RS—•(NAME CHANGE) See *USP Nitrofurazone Related Compound A RS.*•6

Change to read:

USP Norgestrel RS—•Do not dry. Keep container tightly closed.•6

Change to read:

USP Octinoxate RS—•Do not dry. Keep container tightly closed. Store in a cool place. Protect from light.•6

Change to read:

USP Octocrylene RS—•Do not dry. After opening ampul, store in a tightly closed container.•6

Change to read:

USP Oxymetazoline Hydrochloride RS—•Do not dry. Keep container tightly closed.•6

Change to read:

USP Pentobarbital RS—•Do not dry. Keep container tightly closed.•6

Change to read:

USP Phenytoin Related Compound B RS [Diphenylhydantoic acid**]** ($C_{15}H_{12}N_2O_2$ ✧ 252.27)—Do not dry. •Keep container tightly closed. Protect from light.•6

Change to read:

USP Sulfadimethoxine RS—•Do not dry. Keep container tightly closed. Protect from light.•6

Change to read:

■**USP Tiamulin Fumarate RS**—■2S (*USP26*)•Do not dry. Keep container tightly closed. Protect from light.•6

Change to read:

USP Trioxsalen RS—•Do not dry. Keep container tightly closed. Protect from light.•6

Add the following:

•**USP Vitexin RS—**Do not dry. Keep container tightly closed. Protect from light. Store in a cold dry place.•6

Change to read:

USP Zolazepam Hydrochloride RS—Do not dry. ••6 Keep container tightly closed.

Interim Revision Announcement

IN-PROCESS REVISION

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

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

BRIEFING

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

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

•new text•

if slated for an *Interim Revision Announcement to USP 26–NF 21* (*IRA*), thus:

▲new text▲*USP27*

if slated for *USP 27–NF 22*, and thus:

■new text■

if slated for a *Supplement to USP–NF*. The same symbols *not* set off by an extra paragraph break and enclosing text with no increase in type size indicate recent revisions that are already official. Where the symbols appear together with no enclosed text, such as •• or ■■ or ▲▲, it means that text has been deleted and no new text was proposed to replace it. In all revisions, the closing symbol is accompanied by an identifier that indicates the particular *IRA* or *Supplement* or indicates the *USP* or *NF* as the publication where the revision will appear if approved. For example, •2 indicates that the revision is proposed for the *Second Interim Revision Announcement*, and ■2S (*USP 27*) indicates that the proposed revision is slated for the *Second Supplement to USP 27*, and ▲*USP27* and ▲*NF22* indicate that the revisions are proposed for *USP 27* and *NF 22*, respectively.

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

BRIEFING

General Notices and Requirements, *USP 26* page 3, page 3076 of the *Second Supplement*, and page 983 of *PF* 29(4) [July–Aug. 2003]. The proposed revisions in the section *General Chapters* are intended to clarify the intent and character of this section. This change indicates that those chapters numbered over 1000 are intended to be interpretive.

(EC: T. Cecil) RTS—40437-1

Change to read:

"OFFICIAL" AND "OFFICIAL ARTICLES"

The word "official," as used in this Pharmacopeia or with reference hereto, is synonymous with "Pharmacopeial," with "USP," and with "compendial."

The designation "USP" in conjunction with the official title or elsewhere on the label of an article ~~means that the article~~

▲indicates that a monograph is included in the *USP* and that

the article▲*USP27*
purports to comply with

▲all applicable▲*USP27*
USP standards.
~~Any language modifying or limiting this representation shall be accompanied by a statement that the article is "not USP", such specific~~

▲The▲*USP27*
designation

▲"USP"▲*USP27*
on the label

▲may not and▲*USP27*
does not constitute a representation, endorsement, or incorporation by the manufacturer's labeling of the informational material contained in the USP monograph, nor does it constitute assurance by USP that the article is known to comply with USP standards. An article may only purport to comply with a USP standard

▲or other requirements▲*USP27*
when the article is recognized in the *USP*. The standards apply equally to articles bearing the official titles or names derived by transposition of the definitive words of official titles or transposition in the order of the names of two or more active ingredients in official titles, whether or not the added designation "USP" is used. Names considered to be synonyms of the official titles may not be used for official titles.

Although both compendia, the *United States Pharmacopeia* and the *National Formulary*, currently are published under one cover, they remain separate compendia. The designation *USP–NF* or similar combination may be used on the label of an article, provided the label also bears a statement such as, "Meets *NF* standards as published by the USP," indicating the particular compendium to which the article purports to apply.

Where an article differs from the standards of strength, quality, and purity, as determined by the application of the assays and tests set forth for it in the Pharmacopeia, its difference shall be plainly stated on its label. Where an article fails to comply in identity with the identity prescribed in the *USP*, or contains an added substance that interferes with the prescribed assays and tests, such article shall be designated by a name that is clearly distinguishing and differentiating from any name recognized in the Pharmacopeia.

Articles listed herein are official and the standards set forth in the monographs apply to them only when the articles are intended or labeled for use as drugs, as nutritional or dietary supplements, or as medical devices and when bought, sold, or dispensed for these purposes or when labeled as conforming to this Pharmacopeia.

An article is deemed to be recognized in this Pharmacopeia when a monograph for the article is published in it, including its supplements, addenda, or other interim revisions, and an official date is generally or specifically assigned to it.

The following terminology is used for distinguishing the articles for which monographs are provided: an *official substance* is an active drug entity, a recognized nutrient, a dietary supplement ingredient, or a pharmaceutic ingredient (see also *NF 21*) or a component of a finished device for which the monograph title includes no indication of the nature of the finished form; an *official preparation* is a *drug product*, a *nutritional supplement*, a *dietary supplement* or a *finished device*. It is the finished or partially finished (e.g., as in the case of a sterile solid to be constituted into a solution for administration) preparation or product of one or more official substances formulated for use on or for the patient or consumer; an *article* is an item for which a monograph is provided, whether an official substance or an official preparation.

▲*Designating Conformance with Official Standards*—When the letters "USP" or "NF" or "USP–NF" are utilized on the label of an article to indicate compliance with compendial standards, the letters shall appear in conjunction with the official title of the article or when appropriate, with the ingredients contained therein. The letters are not to be enclosed in any symbol such as a circle, square, etc., and must appear in block capital letters.

If a dietary supplement purports to be or is represented as an official product and such claim is determined by USP not to be made in good faith, it is the policy of the USP to seek appropriate legal redress.▲*USP27*

Products Not Marketed in the United States—Interest in the USP outside the United States has always existed. From time to time, monographs may be adopted for articles not legally marketed in the United States as a service to authorities in other countries where USP standards are recognized and applied. Appearance of any such monograph does not grant any marketing rights whatsoever, and the status of the article in the United States must be checked with the U.S. Food and Drug Administration in the event of any question.

Nutritional and Other Dietary Supplements—The designation of an official preparation containing one or more recognized nutrients or dietary supplement ingredients as "USP" or the use of the designation "USP" in conjunction with the title of such nutritional or dietary supplement preparation may be made only if the preparation meets

▲all▲*USP27*
the applicable requirements contained in the individual monograph and general chapters.

▲Any language modifying or limiting this representation shall be accompanied by a statement indicating that the article is "not USP", and indicating how the article differs from the standards of strength, quality, or purity as determined by the application of the tests and assays set forth in the compendia.▲*USP27*
Any additional ingredient in such article that is not recognized in the Pharmacopeia and for which nutritional value is claimed shall not be represented nor imply that such ingredient is of USP quality or recognized by USP. If a preparation does not comply with ▲all▲*USP27*
applicable requirements but contains nutrients or dietary supplement ingredients that are recognized in the *USP*, the article may not designate the individual nutrients or ingredients as complying with USP standards or being of USP quality without designating on the label that the article itself does not comply with USP standards.

Change to read:

SIGNIFICANT FIGURES AND TOLERANCES

Where limits are expressed numerically herein, the upper and lower limits of a range include the two values themselves and all intermediate values, but no values outside the limits. The limits expressed in monograph definitions and tests, regardless of whether the values are expressed as percentages or as absolute numbers, are considered significant to the last digit shown.

Equivalence Statements in Titrimetric Procedures—The directions for titrimetric procedures conclude with a statement of the weight of the analyte that is equivalent to each mL of the standardized titrant. In such an equivalence statement, it is to be understood that the number of significant figures in the concentration of the titrant corresponds to the number of significant figures in the weight of the analyte. Blank corrections are to be made for all titrimetric assays where appropriate (see *Titrimetry* ⟨541⟩).

Tolerances—The limits specified in the monographs for Pharmacopeial articles are established with a view to the use of these articles as drugs, nutritional or dietary supplements, or devices, except where it is indicated otherwise. The use of the molecular formula for the active ingredient(s) named in defining the required strength of a Pharmacopeial article is intended to designate the chemical entity or entities, as given in the complete chemical name of the article, having absolute (100 percent) purity.

A dosage form shall be formulated with the intent to provide 100 percent of the quantity of each ingredient declared on the label.
■■2S (*USP26*)
The tolerances and limits stated in the definitions in the monographs for Pharmacopeial articles allow ■■2S (*USP26*) for analytical error, for unavoidable variations in manufacturing and compounding, and for deterioration to an extent considered acceptable under practical conditions. Where the minimum amount of a substance present in a nutritional or dietary supplement is required to be higher than the lower tolerance limit allowed for in the monograph because of applicable legal requirements, then the upper tolerance limit contained in the monograph shall be increased by a corresponding amount.

The specified tolerances are based upon such attributes of quality as might be expected to characterize an article produced from suitable raw materials under recognized principles of good manufacturing practice.

The existence of compendial limits or tolerances does not constitute a basis for a claim that an official substance that more nearly approaches 100 percent purity "exceeds" the Pharmacopeial quality. Similarly, the fact that an article has been prepared to closer tolerances than those specified in the monograph does not constitute a basis for a claim that the article "exceeds" the Pharmacopeial requirements.

Interpretation of Requirements—Analytical results observed in the laboratory (or calculated from experimental measurements) are compared with stated limits to determine whether there is conformance with compendial assay or test requirements. The observed or calculated values usually will contain more significant figures than there are in the stated limit, and ~~an observed or calculated~~

■a reportable■1S (*USP27*)
result is to be rounded off to the number of places that is in agreement with the limit expression by the following procedure. ~~[NOTE—Limits, which are fixed numbers, are not rounded off.]~~

■Intermediate calculations (e.g., slope for linearity in *Validation of Compendial Methods* ⟨1225⟩) may be rounded for reporting purposes, but the original value (not rounded) should be used for any additional required calculations. Rounding off should not be done until the final calculations for the reportable value have been completed. [NOTE—Limits, which are fixed numbers, are not rounded off.]

A reportable value is often a summary value for several individual determinations. It is the end result of a completed measurement method, as documented. It is the value compared with the acceptance criterion. In most cases, the reportable value is used as documentation for internal or external users.■1S (*USP27*)

When rounding off is required, consider only one digit in the decimal place to the right of the last place in the limit expression. If this digit is smaller than 5, it is eliminated and the preceding digit is unchanged. If this digit is greater than 5, it is eliminated and the preceding digit is increased by one. If this digit equals 5, the 5 is eliminated and the preceding digit is increased by one.

Illustration of Rounding Numerical Values for Comparison with Requirements

Compendial Requirement	Unrounded Value	Rounded Result	Conforms
Assay limit ≥98.0%	97.96%	98.0%	Yes
	97.92%	97.9%	No
	97.95%	98.0%	Yes
Assay limit ≤101.5%	101.55%	101.6%	No
	101.46%	101.5%	Yes
	101.45%	101.5%	Yes
Limit test ≤0.02%	0.025%	0.03%	No
	0.015%	0.02%	Yes
	0.027%	0.03%	No
Limit test ≤3 ppm	0.00035%	0.0004%	No
	0.00025%	0.0003%	Yes
	0.00028%	0.0003%	Yes

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Change to read:

GENERAL CHAPTERS

Each general chapter is assigned a number that appears in brackets adjacent to the chapter name (e.g., ⟨621⟩ *Chromatography*). ~~General chapters that include general *requirements* for tests and assays are numbered from ⟨1⟩ to ⟨999⟩, chapters that are *informational* are numbered from ⟨1000⟩ to ⟨1999⟩, and chapters pertaining to *nutritional supplements* are numbered above ⟨2000⟩.~~

■Articles recognized in this compendia must comply with the official standards and tests and assays in the General Notices, relevant monographs, and General Chapters numbered below 1000. General Chapters numbered above 1000 are considered to be interpretive and are intended to provide information on, give definition to, or describe a particular subject. They contain no official standards, tests, assays, or other mandatory requirements applicable to any pharmacopeial article unless specifically referenced in a monograph or elsewhere in the pharmacopeia.■2S (*USP27*)

The use of the general chapter numbers is encouraged for the identification and rapid access to general tests and information. It is especially helpful where monograph section headings and chapter names are not the same (e.g., *Ultraviolet Absorption* ⟨197U⟩ in a monograph refers to method ⟨197U⟩ under general tests chapter ⟨197⟩ *Spectrophotometric Identification Tests*; *Specific rotation* ⟨781S⟩ in a monograph refers to method ⟨781S⟩ under general tests chapter ⟨781⟩ *Optical Rotation;* and *Calcium* ⟨191⟩ in a monograph refers to the tests for *Calcium* under general tests chapter ⟨191⟩ *Identification Tests—General*).

Change to read:

INGREDIENTS AND PROCESSES

Official drug products and finished devices are prepared from ingredients that meet the requirements of the compendial monographs for those individual ingredients for which monographs are provided (see also *NF 21*). Generally, nutritional and dietary supplements are prepared from ingredients that meet requirements of the compendial monographs for those ingredients for which monographs are provided, except that substances of acceptable food grade quality may be utilized in the event of a difference.

Official substances are prepared according to recognized principles of good manufacturing practice and from ingredients complying with specifications designed to assure that the resultant substances meet the requirements of the compendial monographs (see also *Foreign Substances and Impurities* under *Tests and Assays*).

Preparations for which a complete composition is given in this Pharmacopeia, unless specifically exempted herein or in the individual monograph, are to contain only the ingredients named in the formulas. However, there may be deviation from the specified processes or methods of compounding, though not from the ingredients or proportions thereof, provided the finished preparation conforms to the relevant standards laid down herein and to preparations produced by following the specified process.

The tolerances specified in individual monographs and in the general chapters for compounded preparations are based on those attributes of quality as might be expected to characterize an article compounded from suitable bulk drug substances and ingredients in accordance with the procedures provided or under recognized principles of good pharmaceutical practice as described in this Pharmacopeia (see ■~~*Pharmacy Compounding* ⟨795⟩~~■2S (*USP26*)

▲*Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩)▲*USP27* and elsewhere.

Monographs for preparations intended to be compounded pursuant to prescription may contain assay methods. ■Assay methods■1S (*USP26*) are not intended for evaluating a compounded preparation prior to dispensing. ■Assay■1S (*USP26*) methods are intended to serve as the official test methods in the event of a question or dispute as to whether or not the compounded preparation complies with official standards.

Where a monograph on a preparation calls for an ingredient in an amount expressed on the dried basis, the ingredient need not be dried prior to use if due allowance is made for the water or other volatile substances present in the quantity taken.

Unless specifically exempted elsewhere in this Pharmacopeia, the identity, strength, quality, and purity of an official article are determined by the definition, physical properties, tests, assays, and other specifications relating to the article, whether incorporated in the monograph itself, in the *General Notices*, or in the section *General Chapters*.

Water—Water used as an ingredient of official preparations meets the requirements for *Purified Water*, for *Water for Injection*, or for one of the sterile forms of water covered by a monograph in this Pharmacopeia.

Potable water meeting the requirements for drinking water as set forth in the regulations of the U.S. Environmental Protection Agency may be used in the preparation of official substances.

Alcohol—All statements of percentages of alcohol, such as under the heading *Alcohol content* refer to percentage, by volume, of C_2H_5OH at 15.56°. Where reference is made to "C_2H_5OH," the chemical entity possessing absolute (100 percent) strength is intended.

Alcohol—Where "alcohol" is called for in formulas, tests, and assays, the monograph article *Alcohol* is to be used.

Dehydrated Alcohol—Where "dehydrated alcohol" (absolute alcohol) is called for in tests and assays, the monograph article *Dehydrated Alcohol* is to be used.

Denatured Alcohol—Specially denatured alcohol formulas are available for use in accordance with federal statutes and regulations of the Internal Revenue Service. A suitable formula of specially denatured alcohol may be substituted for Alcohol in the manufacture of Pharmacopeial preparations intended for internal or topical use, provided that the denaturant is volatile and does not remain in the finished product. A finished product that is intended for topical application to the skin may contain specially denatured alcohol, provided that the denaturant is either a normal ingredient or a permissible added substance; in either case the denaturant must be identified on the label of the topical preparation. Where a process is given in the individual monograph, the preparation so made must be identical with that prepared by the given process.

Added Substances—An official substance, as distinguished from an official preparation, contains no added substances except where specifically permitted in the individual monograph. Where such addition is permitted, the label indicates the name(s) and amount(s) of any added substance(s).

Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices*, suitable substances such as antimicrobial agents, bases, carriers, coatings, colors, flavors, preservatives, stabilizers, and vehicles may be added to an official preparation to enhance its stability, usefulness, or elegance or to facilitate its preparation. Such substances are regarded as unsuitable and are prohibited unless (a) they are harmless in the amounts

used, (b) they do not exceed the minimum quantity required to provide their intended effect, (c) their presence does not impair the bioavailability or the therapeutic efficacy or safety of the official preparation, and (d) they do not interfere with the assays and tests prescribed for determining compliance with the Pharmacopeial standards.

Nutritional and Dietary Supplements—Unless otherwise specified in the individual monograph, or elsewhere in the *General Notices*, consistent with applicable regulatory requirements, suitable added substances such as bases, carriers, coatings, colors, flavors, preservatives, and stabilizers may be added to a nutritional supplement preparation to enhance its stability, usefulness, or elegance, or to facilitate its preparation. Such added substances shall be regarded as suitable and shall be permitted unless they interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards.

Additional Ingredients—Additional ingredients, including excipients, may be added to nutritional supplement preparations containing recognized nutrients, consistent with applicable regulatory requirements, provided that they do not interfere with the assays and tests prescribed for determining compliance with Pharmacopeial standards.

Inert Headspace Gases—The air in a container of an article for parenteral use may be evacuated or be replaced by carbon dioxide, helium, or nitrogen, or by a mixture of these gases, which fact need not be declared in the labeling.

Colors—Added substances employed solely to impart color may be incorporated into official preparations, except those intended for parenteral or ophthalmic use, in accordance with the regulations pertaining to the use of colors issued by the FDA provided such added substances are otherwise appropriate in all respects. (See also *Added Substances* under *Injections* ⟨1⟩.)

Ointments and Suppositories—In the preparation of ointments and suppositories, the proportions of the substances constituting the base may be varied to maintain a suitable consistency under different climatic conditions, provided the concentrations of active ingredients are not varied and the bioavailability, therapeutic efficacy or safety of the preparation is not impaired.

Change to read:

TESTS AND ASSAYS

Apparatus—A specification for a definite size or type of container or apparatus in a test or assay is given solely as a recommendation. Where volumetric flasks or other exact measuring, weighing, or sorting devices are specified, this or other equipment of at least equivalent accuracy shall be employed. (See also *Thermometers* ⟨21⟩, *Volumetric Apparatus* ⟨31⟩, and *Weights and Balances* ⟨41⟩.) Where low-actinic or light-resistant containers are specified, clear containers that have been rendered opaque by application of a suitable coating or wrapping may be used.

Where an instrument for physical measurement, such as a spectrophotometer, is specified in a test or assay by its distinctive name, another instrument of equivalent or greater sensitivity and accuracy may be used. In order to obtain solutions having concentrations that are adaptable to the working range of the instrument being used, solutions of proportionately higher or lower concentrations may be prepared according to the solvents and proportions thereof that are specified for the procedure.

Where a particular brand or source of a material, instrument, or piece of equipment, or the name and address of a manufacturer or distributor, is mentioned (ordinarily in a footnote), this identification is furnished solely for informational purposes as a matter of convenience, without implication of approval, endorsement, or certification. Items capable of equal or better performance may be used if these characteristics have been validated.

Where the use of a centrifuge is indicated, unless otherwise specified, the directions are predicated upon the use of apparatus having an effective radius of about 20 cm (8 inches) and driven at a speed sufficient to clarify the supernatant layer within 15 minutes.

Unless otherwise specified, for chromatographic tubes and columns the diameter specified refers to internal diameter (ID); for other types of tubes and tubing the diameter specified refers to outside diameter (OD).

Steam Bath—Where the use of a steam bath is directed, exposure to actively flowing steam or to another form of regulated heat, corresponding in temperature to that of flowing steam, may be used.

Water Bath—Where the use of a water bath is directed without qualification with respect to temperature, a bath of vigorously boiling water is intended.

Foreign Substances and Impurities—Tests for the presence of foreign substances and impurities are provided to limit such substances to amounts that are unobjectionable under conditions in which the article is customarily employed (see also *Impurities in Official Articles* ⟨1086⟩).

While one of the primary objectives of the Pharmacopeia is to assure the user of official articles of their identity, strength, quality, and purity, it is manifestly impossible to include in each monograph a test for every impurity, contaminant, or adulterant that might be present, including microbial contamination. These may arise from a change in the source of material or from a change in the processing, or may be introduced from extraneous sources. Tests suitable for detecting such occurrences, the presence of which is inconsistent with applicable good manufacturing practice or good pharmaceutical practice, should be employed in addition to the tests provided in the individual monograph.

Other Impurities—Official substances may be obtained from more than one process, and thus may contain impurities not considered during preparation of monograph assays or tests. Wherever a monograph includes a chromatographic assay or purity test based on chromatography, other than a test for ~~organic volatile impurities,~~

■residual solvents■1S (*USP27*)

and that monograph does not detect such an impurity, solvents excepted, the impurity shall have its amount and identity, where both are known, stated under the heading *Other Impurity*(*ies*) by the labeling (certificate of analysis) of the official substance.

The presence of any unlabeled impurity in an official substance is a variance from the standard if the content is 0.1% or greater. Tests suitable for detection and quantitating unlabeled impurities, when present as the result of process change or other identifiable, consistent occurrence, shall be submitted to the USP for inclusion in the individual monograph. Otherwise, the impurity shall be identified, preferably by name, and the amount listed under the heading *Other Impurity*(*ies*) in the labeling (certificate of analysis) of the official substance. The sum of all *Other Impurities* combined with the monograph-detected impurities does not exceed 2.0% (see *Ordinary Impurities* ⟨466⟩), unless otherwise stated in the monograph.

Categories of drug substances excluded from *Other Impurities* requirements are fermentation products and semi-synthetics derived therefrom, radiopharmaceuticals, biologics, biotechnology-derived products, peptides, herbals, and crude products of animal or plant origin. Any substance known to be toxic must not be listed under *Other Impurities*.

■**Residual Solvents**—The requirements are stated in *Organic Volatile Impurities* ⟨467⟩ together with information in *Impurities in Official Articles* ⟨1086⟩. Thus all drug substances, excipients, and products are subject to relevant control of residual solvents, even when no test is specified in the

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individual monograph. The requirements have been aligned with the ICH guideline on this topic. If solvents are used during production, they are of suitable quality. In addition, the toxicity and residual level of each solvent are taken into consideration, and the solvents are limited according to the principles defined and the requirements specified in *Organic Volatile Impurities* ⟨467⟩, using the general methods presented therein or other suitable methods.■1S (*USP27*)

Procedures—Assay and test procedures are provided for determining compliance with the Pharmacopeial standards of identity, strength, quality, and purity.

In performing the assay or test procedures in this Pharmacopeia, it is expected that safe laboratory practices will be followed. This includes the utilization of precautionary measures, protective equipment, and work practices consistent with the chemicals and procedures utilized. Prior to undertaking any assay or procedure described in this Pharmacopeia, the individual should be aware of the hazards associated with the chemicals and the procedures and means of protecting against them. This Pharmacopeia is not designed to describe such hazards or protective measures.

Every compendial article in commerce shall be so constituted that when examined in accordance with these assay and test procedures, it meets all of the requirements in the monograph defining it. However, it is not to be inferred that application of every analytical procedure in the monograph to samples from every production batch is necessarily a prerequisite for assuring compliance with Pharmacopeial standards before the batch is released for distribution. Data derived from manufacturing *process validation* studies and from *in-process controls* may provide greater assurance that a batch meets a particular monograph requirement than analytical data derived from an examination of finished units drawn from that batch. On the basis of such assurances, the analytical procedures in the monograph may be omitted by the manufacturer in judging compliance of the batch with the Pharmacopeial standards.

Automated procedures employing the same basic chemistry as those assay and test procedures given in the monograph are recognized as being equivalent in their suitability for determining compliance. Conversely, where an automated procedure is given in the monograph, manual procedures employing the same basic chemistry are recognized as being equivalent in their suitability for determining compliance. Compliance may be determined also by the use of alternative methods, chosen for advantages in accuracy, sensitivity, precision, selectivity, or adaptability to automation or computerized data reduction or in other special circumstances. Such alternative or automated procedures or methods shall be validated. However, Pharmacopeial standards and procedures are interrelated; therefore, where a difference appears or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.

In the performance of assay or test procedures, not less than the specified number of dosage units should be taken for analysis. Proportionately larger or smaller quantities than the specified weights and volumes of assay or test substances and Reference Standards may be taken, provided the measurement is made with at least equivalent accuracy and provided that any subsequent steps, such as dilutions, are adjusted accordingly to yield concentrations equivalent to those specified and are made in such manner as to provide at least equivalent accuracy. To minimize environmental impact or contact with hazardous materials, apparatus and chemicals specified in Pharmacopeial procedures also may be proportionally changed.

Where it is directed in an assay or a test that a certain quantity of substance or a counted number of dosage units is to be examined, the specified quantity or number is a minimal figure (the singlet determination) chosen only for convenience of analytical manipulation; it is not intended to restrict the total quantity of substance or number of units that may be subjected to the assay or test or that should be tested in accordance with good manufacturing practices.

Where it is directed in the assay of Tablets to "weigh and finely powder not fewer than" a given number, usually 20, of the Tablets, it is intended that a counted number of Tablets shall be weighed and reduced to a powder. The portion of the powdered tablets taken for assay is representative of the whole Tablets and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Tablet by multiplying this result by the average Tablet weight and dividing by the weight of the portion taken for the assay.

Similarly, where it is directed in the assay of Capsules to remove, as completely as possible, the contents of not less than a given number, usually 20, of the Capsules, it is intended that a counted number of Capsules should be carefully opened and the contents quantitatively removed, combined, mixed, and weighed accurately. The portion of mixed Capsules contents taken for the assay is representative of the contents of the Capsules and is, in turn, weighed accurately. The result of the assay is then related to the amount of active ingredient per Capsule by multiplying this result by the average weight of Capsule content and dividing by the weight of the portion taken for the assay.

Where the definition in a monograph states the tolerances as being "calculated on the dried (or anhydrous or ignited) basis," the directions for drying or igniting the sample prior to assaying are generally omitted from the *Assay* procedure. Assay and test procedures may be performed on the undried or unignited substance and the results calculated on the dried, anhydrous, or ignited basis, provided a test for *Loss on drying*, or *Water*, or *Loss on ignition*, respectively, is given in the monograph. Where the presence of moisture or other volatile material may interfere with the procedure, previous drying of the substance is specified in the individual monograph and is obligatory.

Throughout a monograph that includes a test for *Loss on drying* or *Water*, the expression "previously dried" without qualification signifies that the substance is to be dried as directed under *Loss on drying* or *Water* (gravimetric determination).

Unless otherwise directed in the test or assay in the individual monograph or in a general chapter, USP Reference Standards are to be dried before use, or used without prior drying, specifically in accordance with the instructions given in the chapter *USP Reference Standards* ⟨11⟩, and on the label of the Reference Standard. Where the label instructions differ in detail from those in the chapter, the label text is determinative.

In stating the appropriate quantities to be taken for assays and tests, the use of the word "about" indicates a quantity within 10% of the specified weight or volume. However, the weight or volume taken is accurately determined and the calculated result is based upon the exact amount taken. The same tolerance applies to specified dimensions.

Where the use of a pipet is directed for measuring a specimen or an aliquot in conducting a test or an assay, the pipet conforms to the standards set forth under *Volumetric Apparatus* ⟨31⟩, and is to be used in such manner that the error does not exceed the limit stated for a pipet of its size. Where a pipet is specified, a suitable buret, conforming to the standards set forth under *Volumetric Apparatus* ⟨31⟩ , may be substituted. Where a "to contain" pipet is specified, a suitable volumetric flask may be substituted.

Expressions such as "25.0 mL" and "25.0 mg," used with respect to volumetric or gravimetric measurements, indicate that the quantity is to be "accurately measured" or "accurately weighed" within the limits stated under *Volumetric Apparatus* ⟨31⟩ or under *Weights and Balances* ⟨41⟩.

The term "transfer" is used generally to specify a quantitative manipulation.

The term "concomitantly," used in such expressions as "concomitantly determine" or "concomitantly measured," in directions for assays and tests, is intended to denote that the determinations or measurements are to be performed in immediate succession. See also *Use of Reference Standards* under *Spectrophotometry and Light-Scattering* ⟨851⟩.

Blank Determination—Where it is directed that "any necessary correction" be made by a blank determination, the determination is to be conducted using the same quantities of the same reagents treated in the same manner as the solution or mixture containing the portion of the substance under assay or test, but with the substance itself omitted.

Desiccator—The expression "in a desiccator" specifies the use of a tightly closed container of suitable size and design that maintains an atmosphere of low moisture content by means of silica gel or other suitable desiccant.

A "vacuum desiccator" is one that maintains the low-moisture atmosphere at a reduced pressure of not more than 20 mm of mercury or at the pressure designated in the individual monograph.

Dilution—Where it is directed that a solution be diluted "quantitatively and stepwise," an accurately measured portion is to be diluted by adding water or other solvent, in the proportion indicated, in one or more steps. The choice of apparatus to be used should take into account the relatively larger errors generally associated with using small-volume volumetric apparatus (see *Volumetric Apparatus* ⟨31⟩).

Drying to Constant Weight—The specification "dried to constant weight" means that the drying shall be continued until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional hour of drying.

Filtration—Where it is directed to "filter," without further qualification, the intent is that the liquid be filtered through suitable filter paper or equivalent device until the filtrate is clear.

Identification Tests—The Pharmacopeial tests headed *Identification* are provided as an aid in verifying the identity of articles as they are purported to be, such as those taken from labeled containers. Such tests, however specific, are not necessarily sufficient to establish proof of identity; but failure of an article taken from a labeled container to meet the requirements of a prescribed identification test indicates that the article may be mislabeled. Other tests and specifications in the monograph often contribute to establishing or confirming the identity of the article under examination.

Ignition to Constant Weight—The specification "ignite to constant weight" means that the ignition shall be continued, at 800 ± 25° unless otherwise indicated, until two consecutive weighings do not differ by more than 0.50 mg per g of substance taken, the second weighing following an additional 15-minute ignition period.

Indicators—Where the use of a test solution ("TS") as an indicator is specified in a test or an assay, approximately 0.2 mL, or 3 drops, of the solution shall be added, unless otherwise directed.

Logarithms—Logarithms used in the assays are to the base 10.

Microbial Strains—Where a microbial strain is cited and identified by its ATCC catalog number, the specified strain shall be used directly or, if subcultured, shall be used not more than five passages removed from the original strain.

Negligible—This term indicates a quantity not exceeding 0.50 mg.

Odor—Terms such as "odorless," "practically odorless," "a faint characteristic odor," or variations thereof, apply to examination, after exposure to the air for 15 minutes, of either a freshly opened package of the article (for packages containing not more than 25 g) or (for larger packages) of a portion of about 25 g of the article that has been removed from its package to an open evaporating dish of about 100-mL capacity. An odor designation is descriptive only and is not to be regarded as a standard of purity for a particular lot of an article.

Pressure Measurements—The term "mm of mercury" used with respect to measurements of blood pressure, pressure within an apparatus, or atmospheric pressure refers to the use of a suitable manometer or barometer calibrated in terms of the pressure exerted by a column of mercury of the stated height.

Solutions—Unless otherwise specified in the individual monograph, all solutions called for in tests and assays are prepared with *Purified Water*.

An expression such as "(1 in 10)" means that 1 part *by volume* of a liquid is to be diluted with, or 1 part *by weight* of a solid is to be dissolved in, sufficient of the diluent or solvent to make the volume of the finished solution 10 parts *by volume*.

An expression such as "(20:5:2)" means that the respective numbers of parts, by volume, of the designated liquids are to be mixed, unless otherwise indicated.

The notation "VS" after a specified volumetric solution indicates that such solution is standardized in accordance with directions given in the individual monograph or under *Volumetric Solutions* in the section *Reagents, Indicators, and Solutions*, and is thus differentiated from solutions of approximate normality or molarity.

Where a standardized solution of a specific concentration is called for in a test or an assay, a solution of other normality or molarity may be used, provided allowance is made for the difference in concentration and provided the error of measurement is not increased thereby.

Specific Gravity—Unless otherwise stated, the specific gravity basis is 25°/25°, i.e., the ratio of the weight of a substance in air at 25° to the weight of an equal volume of water at the same temperature.

Temperatures—Unless otherwise specified, all temperatures in this Pharmacopeia are expressed in centigrade (Celsius) degrees, and all measurements are made at 25°. Where moderate heat is specified, any temperature not higher than 45° (113°F) is indicated. See *Storage Temperature* under *Preservation, Packaging, Storage, and Labeling* for other definitions.

Time Limit—In the conduct of tests and assays, 5 minutes shall be allowed for the reaction to take place unless otherwise specified.

Vacuum—The term "in vacuum" denotes exposure to a pressure of less than 20 mm of mercury unless otherwise indicated.

Where drying in vacuum over a desiccant is directed in the individual monograph, a vacuum desiccator or a vacuum drying pistol, or other suitable vacuum drying apparatus, is to be used.

Water—Where water is called for in tests and assays, Purified Water is to be used unless otherwise specified. For special kinds of water such as "carbon dioxide–free water," see the introduction to the section *Reagents, Indicators, and Solutions*. For *High-purity Water* see *Containers* ⟨661⟩.

Water and Loss on Drying—Where the water of hydration or adsorbed water of a Pharmacopeial article is determined by the titrimetric method, the test is generally given under the heading *Water*. Monograph limits expressed as a percentage are figured on a weight/weight basis unless otherwise specified. Where the determination is made by drying under specified conditions, the test is generally given under the heading *Loss on drying*. However, *Loss on drying* is most often given as the heading where the loss in weight is known to represent residual volatile constituents including organic solvents as well as water.

Test Results, Statistics, and Standards—Interpretation of results from official tests and assays requires an understanding of the nature and style of compendial standards, in addition to an understanding of the scientific and mathematical aspects of laboratory analysis and quality assurance for analytical laboratories.

Confusion of compendial standards with release tests and with statistical sampling plans occasionally occurs. Compendial standards define what is an acceptable article and give test procedures that demonstrate that the article is in compliance. These standards apply at any time in the life of the article from production to consumption. The manufacturer's release specifications, and compliance with good manufacturing practices generally, are developed and followed to assure that the article will indeed comply with

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compendial standards until its expiration date, when stored as directed. Thus, when tested from the viewpoint of commercial or regulatory compliance, any specimen tested as directed in the monograph for that article shall comply.

Tests and assays in this Pharmacopeia prescribe operation on a single specimen, that is, the singlet determination, which is the minimum sample on which the attributes of a compendial article should be measured. Some tests, such as those for *Dissolution* and *Uniformity of dosage units*, require multiple dosage units in conjunction with a decision scheme. These tests, albeit using a number of dosage units, are in fact the singlet determinations of those particular attributes of the specimen. These procedures should not be confused with statistical sampling plans. Repeats, replicates, statistical rejection of outliers, or extrapolations of results to larger populations are neither specified nor proscribed by the compendia; such decisions are dependent on the objectives of the testing. Commercial or regulatory compliance testing, or manufacturer's release testing, may or may not require examination of additional specimens, in accordance with predetermined guidelines or sampling strategies. Treatments of data handling are available from organizations such as ISO, IUPAC, and AOAC.

■Where the *Content Uniformity* determinations have been made using the same ~~method~~ procedure specified in the *Assay*, the average of all of the individual *Content Uniformity* determinations may be used as the *Assay* value.■1S (*USP27*)

Description—Information on the "description" pertaining to an article, which is relatively general in nature, is provided in the reference table *Description and Relative Solubility of USP and NF Articles* in this Pharmacopeia for those who use, prepare, and dispense drugs and/or related articles, solely to indicate properties of an article complying with monograph standards. The properties are not in themselves standards or tests for purity even though they may indirectly assist in the preliminary evaluation of an article.

Solubility—The statements concerning solubilities given in the reference table *Description and Relative Solubility of USP and NF Articles* for Pharmacopeial articles are not standards or tests for purity but are provided primarily as information for those who use, prepare, and dispense drugs and/or related articles. Only where a quantitative solubility test is given, and is designated as such, is it a test for purity.

The approximate solubilities of Pharmacopeial substances are indicated by the descriptive terms in the accompanying table. Soluble Pharmacopeial articles, when brought into solution, may show traces of physical impurities, such as minute fragments of filter paper, fibers, and other particulate matter, unless limited or excluded by definite tests or other specifications in the individual monographs.

Descriptive Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1000
Very slightly soluble	From 1000 to 10,000
Practically insoluble, or Insoluble	Greater than or equal to 10,000

▲**Interchangeable Methods**—Certain general chapters contain a statement that the text in question is harmonized with the corresponding text of the *European Pharmacopoeia* and/or the *Japanese Pharmacopoeia* and that these texts are interchangeable. Therefore, if a substance or preparation is found to comply with a requirement using an interchangeable method from one of these pharmacopeias, it should comply with the requirements of the *United States Pharmacopeia*. However, where a difference appears, or in the event of dispute, only the result obtained by the procedure given in this Pharmacopeia is conclusive.▲*USP26*

Change to read:

PRESERVATION, PACKAGING, STORAGE, AND LABELING

Containers—The *container* is that which holds the article and is or may be in direct contact with the article. The *immediate container* is that which is in direct contact with the article at all times. The *closure* is a part of the container.

Prior to its being filled, the container should be clean. Special precautions and cleaning procedures may be necessary to ensure that each container is clean and that extraneous matter is not introduced into or onto the article.

The container does not interact physically or chemically with the article placed in it so as to alter the strength, quality, or purity of the article beyond the official requirements.

The Pharmacopeial requirements for the use of specified containers apply also to articles as packaged by the pharmacist or other dispenser, unless otherwise indicated in the individual monograph.

■*Tamper-Evident*■2S (*USP26*) *Packaging*—The container or individual carton of a sterile article intended for ophthalmic or otic use, except where extemporaneously compounded for immediate dispensing on prescription, shall be so sealed that the contents cannot be used without obvious destruction of the seal.

Articles intended for sale without prescription are also required to comply with the ■tamper-evident■2S (*USP26*) packaging and labeling requirements of the FDA where applicable.

Preferably, the immediate container and/or the outer container or protective packaging utilized by a manufacturer or distributor for all dosage forms that are not specifically exempt is designed so as to show evidence of any tampering with the contents.

Light-Resistant Container (see *Light Transmission* under *Containers* ⟨661⟩)—A light-resistant container protects the contents from the effects of light by virtue of the specific properties of the material of which it is composed, including any coating applied to it. Alternatively, a clear and colorless or a translucent container may be made light-resistant by means of an opaque covering, in which case the label of the container bears a statement that the opaque covering is needed until the contents are to be used or administered. Where it is directed to "protect from light" in an individual monograph, preservation in a light-resistant container is intended.

Where an article is required to be packaged in a light-resistant container, and if the container is made light-resistant by means of an opaque covering, a single-use, unit-dose container or mnemonic pack for dispensing may not be removed from the outer opaque covering prior to dispensing.

Well-Closed Container—A well-closed container protects the contents from extraneous solids and from loss of the article under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Tight Container—A tight container protects the contents from contamination by extraneous liquids, solids, or vapors, from loss of the article, and from efflorescence, deliquescence, or evaporation under the ordinary or customary conditions of handling, shipment, storage, and distribution, and is capable of tight reclosure. Where a tight container is specified, it may be replaced by a hermetic container for a single dose of an article.

A gas cylinder is a metallic container designed to hold a gas under pressure. As a safety measure, for carbon dioxide, cyclopropane, helium, nitrous oxide, and oxygen, the Pin-index Safety System of matched fittings is recommended for cylinders of Size E or smaller.

NOTE—Where packaging and storage in a *tight container* or a *well-closed container* is specified in the individual monograph, the container utilized for an article when dispensed on prescription meets the requirements under *Containers—Permeation* ⟨671⟩.

Hermetic Container—A hermetic container is impervious to air or any other gas under the ordinary or customary conditions of handling, shipment, storage, and distribution.

Single-Unit Container—A single-unit container is one that is designed to hold a quantity of drug product intended for administration as a single dose or a single finished device intended for use promptly after the container is opened. Preferably, the immediate container and/or the outer container or protective packaging shall be so designed as to show evidence of any tampering with the contents. Each single-unit container shall be labeled to indicate the identity, quantity and/or strength, name of the manufacturer, lot number, and expiration date of the article.

Single-Dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A single-dose container is a single-unit container for articles intended for parenteral administration only. A single-dose container is labeled as such. Examples of single-dose containers include prefilled syringes, cartridges, fusion-sealed containers, and closure-sealed containers when so labeled.

Unit-Dose Container—A unit-dose container is a single-unit container for articles intended for administration by other than the parenteral route as a single dose, direct from the container.

Unit-of-Use Container—A unit-of-use container is one that contains a specific quantity of a drug product and that is intended to be dispensed as such without further modification except for the addition of appropriate labeling. A unit-of-use container is labeled as such.

Multiple-Unit Container—A multiple-unit container is a container that permits withdrawal of successive portions of the contents without changing the strength, quality, or purity of the remaining portion.

Multiple-Dose Container (see also *Containers for Injections* under *Injections* ⟨1⟩)—A multiple-dose container is a multiple-unit container for articles intended for parenteral administration only.

Storage Temperature and Humidity—Specific directions are stated in some monographs with respect to the temperatures and humidity at which Pharmacopeial articles shall be stored and distributed (including the shipment of articles to the consumer) when stability data indicate that storage and distribution at a lower or a higher temperature and a higher humidity produce undesirable results. Such directions apply except where the label on an article states a different storage temperature on the basis of stability studies of that particular formulation. Where no specific storage directions or limitations are provided in the individual monograph, but the label of an article states a storage temperature that is based on stability studies of that particular formulation, such labeled storage directions apply (see also *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩.) The conditions are defined by the following terms.

Freezer—A place in which the temperature is maintained thermostatically between –25° and –10° (–13° and 14 °F).

Cold—Any temperature not exceeding 8° (46 °F). A *refrigerator* is a cold place in which the temperature is maintained thermostatically between 2° and 8° (36° and 46 °F).

Cool—Any temperature between 8° and 15° (46° and 59 °F). An article for which storage in a *cool place* is directed may, alternatively, be stored and distributed in a *refrigerator*, unless otherwise specified by the individual monograph.

Room Temperature—The temperature prevailing in a working area.

Controlled Room Temperature—A temperature maintained thermostatically that encompasses the usual and customary working environment of 20° to 25° (68° to 77 °F); that results in a mean kinetic temperature calculated to be not more than 25°; and that allows for excursions between 15° and 30° (59° and 86 °F) that are experienced in pharmacies, hospitals, and warehouses. Provided the mean kinetic temperature remains in the allowed range, transient spikes up to 40° are permitted as long as they do not exceed 24 hours. Spikes above 40° may be permitted if the manufacturer so instructs. Articles may be labeled for storage at "controlled room temperature" or at "up to 25°", or other wording based on the same mean kinetic temperature. The mean kinetic temperature is a calculated value that may be used as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variations. (See also *Stability* under *Pharmaceutical Dosage Forms* ⟨1151⟩.)

An article for which storage at *Controlled room temperature* is directed may, alternatively, be stored and distributed in a *cool place*, unless otherwise specified in the individual monograph or on the label.

Warm—Any temperature between 30° and 40° (86° and 104 °F).

Excessive Heat—Any temperature above 40° (104 °F).

Protection from Freezing—Where, in addition to the risk of breakage of the container, freezing subjects an article to loss of strength or potency, or to destructive alteration of its characteristics, the container label bears an appropriate instruction to protect the article from freezing.

Dry Place—The term "dry place" denotes a place that does not exceed 40% average relative humidity at *Controlled Room Temperature* or the equivalent water vapor pressure at other temperatures. The determination may be made by direct measurement at the place or may be based on reported climatic conditions. Determination is based on not less than 12 equally spaced measurements that encompass either a season, a year, or, where recorded data demonstrate, the storage period of the article. There may be values of up to 45% relative humidity provided that the average value is 40% relative humidity.

Storage in a container validated to protect the article from moisture vapor, including storage in bulk, is considered a dry place.

Storage under Nonspecific Conditions—~~For articles, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution include protection from moisture, freezing, and excessive heat.~~

▲Where no specific directions or limitations are provided in the packaging and storage section of individual monographs or in the article's labeling, the conditions of storage shall include storage at controlled room temperature, protection from moisture, and, where necessary, protection from light. Articles shall be protected from moisture, freezing, and excessive heat, and, where necessary, from light during shipping and distribution. Active pharmaceutical ingredients are exempt from this requirement.▲*USP27*

■**Repackaging Instructions—**Except where a drug product is packaged in a container intended to be dispensed directly to the patient, such as a unit-of-use or unit-dose container, the labeling shall contain directions specifying the types of containers suitable for repackaging the drug product so as to maintain its identity, strength, quality, and

In-Process Revision

purity. Such directions shall be sufficient to allow a repackager or dispenser to select an adequate container and shall include a description of the composition of the container(s), e.g., glass, polyethylene, polyvinyl chloride, and any moisture vapor transmission rate characteristics required. The labeling shall also indicate whether or not the container is to afford light protection, and shall include any storage or shipping temperature restrictions to which the drug as repackaged shall be limited (see 21 CFR 201.100).■1S (*USP27*)

Labeling—The term "labeling" designates all labels and other written, printed, or graphic matter upon an immediate container of an article or upon, or in, any package or wrapper in which it is enclosed, except any outer shipping container. The term "label" designates that part of the labeling upon the immediate container.

A shipping container containing a single article, unless such container is also essentially the immediate container or the outside of the consumer package, is labeled with a minimum of product identification (except for controlled articles), lot number, expiration date, and conditions for storage and distribution.

Articles in this Pharmacopeia are subject to compliance with such labeling requirements as may be promulgated by governmental bodies in addition to the Pharmacopeial requirements set forth for the articles.

Amount of Ingredient per Dosage Unit—The strength of a drug product is expressed on the container label in terms of micrograms or milligrams or grams or percentage of the therapeutically active moiety or drug substance, whichever form is used in the title, unless otherwise indicated in an individual monograph. Both the active moiety and drug substance names and their equivalent amounts are then provided in the labeling.

Pharmacopeial articles in capsule, tablet, or other unit dosage form shall be labeled to express the quantity of each active ingredient or recognized nutrient contained in each such unit; except that, in the case of unit-dose oral solutions or suspensions, whether supplied as liquid preparations or as liquid preparations that are constituted from solids upon addition of a designated volume of a specific diluent, the label shall express the quantity of each active ingredient or recognized nutrient delivered under the conditions prescribed in *Deliverable Volume* ⟨698⟩. Pharmacopeial drug products not in unit dosage form shall be labeled to express the quantity of each active ingredient in each milliliter or in each gram, or to express the percentage of each such ingredient (see *Percentage Measurements*), except that oral liquids or solids intended to be constituted to yield oral liquids may, alternatively, be labeled in terms of each 5-mL portion of the liquid or resulting liquid. Unless otherwise indicated in a monograph or chapter, such declarations of strength or quantity shall be stated only in metric units (see also *Units of Potency* in these *General Notices*).

Use of Leading and Terminal Zeros—In order to help minimize the possibility of errors in the dispensing and administration of drugs, the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero (e.g., express as 4 mg [not 4.0 mg]). The quantity of active ingredient when expressed as a decimal number smaller than one shall be shown with a zero preceding the decimal point (e.g., express as 0.2 mg [not .2 mg]).

Labeling of Salts of Drugs—It is an established principle that Pharmacopeial articles shall have only one official name. For purposes of saving space on labels, and because chemical symbols for the most common inorganic salts of drugs are well known to practitioners as synonymous with the written forms, the following alternatives are permitted in labeling official articles that are salts: HCl for hydrochloride; HBr for hydrobromide; Na for sodium; and K for potassium. The symbols Na and K are intended for use in abbreviating names of the salts of organic acids; but these symbols are not used where the word Sodium or Potassium appears at the beginning of an official title (e.g., Phenobarbital Na is acceptable, but Na Salicylate is not to be written).

Labeling Vitamin-Containing Products—The vitamin content of an official drug product shall be stated on the label in metric units per dosage unit. The amounts of vitamins A, D, and E may be stated also in USP Units. Quantities of vitamin A declared in metric units refer to the equivalent amounts of retinol (vitamin A alcohol). The label of a nutritional supplement shall bear an identifying lot number, control number, or batch number.

Labeling Parenteral and Topical Preparations—The label of a preparation intended for parenteral or topical use states the names of all added substances (see *Added Substances* in these *General Notices and Requirements*, and see *Labeling* under *Injections* ⟨1⟩), and, in the case of parenteral preparations, also their amounts or proportions, except that for substances added for adjustment of pH or to achieve isotonicity, the label may indicate only their presence and the reason for their addition.

Labeling Electrolytes—The concentration and dosage of electrolytes for replacement therapy (e.g., sodium chloride or potassium chloride) shall be stated on the label in milliequivalents (mEq). The label of the product shall indicate also the quantity of ingredient(s) in terms of weight or percentage concentration.

Labeling Alcohol—The content of alcohol in a liquid preparation shall be stated on the label as a percentage (v/v) of C_2H_5OH.

Special Capsules and Tablets—The label of any form of Capsule or Tablet intended for administration other than by swallowing intact bears a prominent indication of the manner in which it is to be used.

Expiration Date and Beyond-Use Date—The label of an official drug product, nutritional or dietary supplement product shall bear an expiration date. All articles shall display the expiration date so that it can be read by an ordinary individual under customary conditions of purchase and use. The expiration date shall be prominently displayed in high contrast to the background or sharply embossed, and easily understood (e.g., "EXP 6/89," "Exp. June 89," or "Expires 6/89"). [NOTE—For additional information and guidance, refer to the Nonprescription Drug Manufacturers Association's *Voluntary Codes and Guidelines of the OTC Medicines Industry.*]

The monographs for some preparations state how the expiration date that shall appear on the label is to be determined. In the absence of a specific requirement in the individual monograph for a drug product or nutritional supplement, the label shall bear an expiration date assigned for the particular formulation and package of the article, with the following exception: the label need not show an expiration date in the case of a drug product or nutritional supplement packaged in a container that is intended for sale without prescription and the labeling of which states no dosage limitations, and which is stable for not less than 3 years when stored under the prescribed conditions.

Where an official article is required to bear an expiration date, such article shall be dispensed solely in, or from, a container labeled with an expiration date, and the date on which the article is dispensed shall be within the labeled expiry period. The expiration date identifies the time during which the article may be expected to meet the requirements of the Pharmacopeial monograph, provided it is kept under the prescribed storage conditions. The expiration date limits the time during which the article may be dispensed or used. Where an expiration date is stated only in terms of the month and the year, it is a representation that the intended expiration date is the last day of the stated month. The beyond-use date is the date after which an article must not be used. The dispenser shall place on the label of the prescription container a suitable beyond-use date to limit the patient's use of the article based on any information supplied by the manufacturer and the

General Notices and Requirements of this Pharmacopeia. The beyond-use date placed on the label shall not be later than the expiration date on the manufacturer's container.

For articles requiring constitution prior to use, a suitable beyond-use date for the constituted product shall be identified in the labeling.

For all other dosage forms, in determining an appropriate period of time during which a prescription drug may be retained by a patient after its dispensing, the dispenser shall take into account, in addition to any other relevant factors, the nature of the drug; the container in which it was packaged by the manufacturer and the expiration date thereon; the characteristics of the patient's container, if the article is repackaged for dispensing; the expected storage conditions to which the article may be exposed; any unusual storage conditions to which the article may be exposed; and the expected length of time of the course of therapy. The dispenser shall, on taking into account the foregoing, place on the label of a multiple-unit container a suitable beyond-use date to limit the patient's use of the article. Unless otherwise specified in the individual monograph, or in the absence of stability data to the contrary, such beyond-use date shall be not later than (a) the expiration date on the manufacturer's container, or (b) one year from the date the drug is dispensed, whichever is earlier. For nonsterile solid and liquid dosage forms that are packaged in single-unit and unit-dose containers, the beyond-use date shall be one year from the date the drug is packaged into the single-unit or unit-dose container or the expiration date on the manufacturers container, whichever is earlier, unless stability data or the manufacturers labeling indicates otherwise.

The dispenser must maintain the facility where the dosage forms are packaged and stored, at a temperature such that the mean kinetic temperature is not greater than 25°. The plastic material used in packaging the dosage forms must afford better protection than polyvinyl chloride, which does not provide adequate protection against moisture permeation. Records must be kept of the temperature of the facility where the dosage forms are stored, and of the plastic materials used in packaging.

Pharmaceutical Compounding—The label on the container or package of an official compounded preparation shall bear a beyond-use date. The beyond-use date is the date after which a compounded preparation is not to be used. Because compounded preparations are intended for administration immediately or following short-term storage, their beyond-use dates may be assigned based on criteria different from those applied to assigning expiration dates to manufactured drug products.

The monograph for an official compounded preparation typically includes a beyond-use requirement that states the time period following the date of compounding during which the preparation, properly stored, is to be used. In the absence of stability information that is applicable to a specific drug and preparation, recommendations for maximum beyond-use dates have been devised for nonsterile compounded drug preparations that are packaged in tight, light-resistant containers and stored at controlled room temperature unless otherwise indicated (see *Stability Criteria and Beyond-Use Dating* under *Stability of Compounded Preparations* in the general tests chapter ■~~*Pharmacy Compounding* ⟨795⟩~~:■2S (*USP26*)

▲*Pharmaceutical Compounding—Nonsterile Preparations* ⟨795⟩).▲*USP27*

MONOGRAPHS (USP)

BRIEFING

Acepromazine Maleate, *USP 26* page 14; **Alteplase,** *USP 26* page 69; **Aminopentamide Sulfate,** *USP 26* page 123; **Azaperone,** *USP 26* page 195; **Desoxycorticosterone Pivalate,** *USP 26* page 557; **Flunixin Meglumine,** *USP 26* page 799; **Glucagon,** *USP 26* page 861; **Indigotindisulfonate Sodium,** *USP 26* page 961; **Indocyanine Green,** *USP 26* page 966; **Insulin,** *USP 26* page 973 and page 2969 of the *First Supplement;* **Insulin Human,** *USP 26* page 976; **Ketamine Hydrochloride,** *USP 26* page 1045; **Manganese Sulfate,** *USP 26* page 1125; **Menotropins,** *USP 26* page 1148; **Oxytocin,** *USP 26* page 1385; **Phenylbutazone Injection,** *USP 26* page 1457; **Vasopressin,** *USP 26* page 1923; **Xylazine,** *USP 26* page 1942 and page 3002 of the *First Supplement;* **Xylazine Hydrochloride,** *USP 26* page1944; **Yohimbine Hydrochloride,** *USP 26* page 1947 and page 3003 of the *First Supplement.* Revisions are proposed to establish consistency with the system of *Labeling* established in 1993 by the USP Drug Nomenclature Committee (page 5618 of *PF* 19(4) [July–Aug. 1993]). Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms, a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that where the label states that it is sterile it must meet the requirements under *Sterility Test* ⟨71⟩ and *Bacterial Endotoxins* ⟨85⟩. In addition, where the label states that it must be subjected to further processing during the preparation of injectable dosage forms, it must meet the requirements under *Bacterial Endotoxins* ⟨85⟩. In some monographs it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(BNT, GTB, VET: I. DeVeau; PSD: C. Okeke) RTS—40270-1

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate that it is for veterinary use only.

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

In-Process Revision

Add the following:

■**Other requirements—**Where the label states that Acepromazine Maleate is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Acyclovir, *USP 26* page 47; **Chloroquine,** *USP 26* page 423; **Ciprofloxacin,** *USP 26* page 457 and page 2951 of the *First Supplement;* **Ciprofloxacin Hydrochloride,** *USP 26* page 458; **Cupric Chloride,** *USP 26* page 522; **Cupric Sulfate,** *USP 26* page 524; **Emetine Hydrochloride,** *USP 26* page 699; **Floxuridine,** *USP 26* page 793; **Ganciclovir,** page 2966 of the *First Supplement;* **Glycerin,** *USP 26* page 867; **Isoniazid,** *USP 26* page 1025; **Metronidazole,** *USP 26* page 1226; **Miconazole,** *USP 26* page 1234; **Ofloxacin,** *USP 26* page 1347; **Sulfadiazine Sodium,** *USP 26* page 1731; **Sulfamethoxazole,** *USP 26* page 1737; **Trimethoprim,** *USP 26* page 1893 and page 1080 of *PF* 29(4) [July–Aug. 2003]; **Trimethoprim Sulfate,** *USP 26* page 1894; **Zidovudine,** *USP 26* page 1950. Revisions are proposed to establish consistency with the system of *Labeling* established in 1993 by the USP Drug Nomenclature Committee (see page 5618 of *PF* 19(4) [July–Aug. 1993]). Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms, a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that where the label states that it is sterile, it must meet the requirements of the *Sterility Test* ⟨71⟩ and of the test for *Bacterial Endotoxins* ⟨85⟩. In addition where the label states that it must be subjected to further processing during the preparation of injectable dosage forms, it must meet the requirements of the test for *Bacterial Endotoxins* ⟨85⟩. In some monographs it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-1

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Acyclovir RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Acyclovir Oral Suspension, *USP 26* page 49 and page 604 of *PF* 29 (3) [May–June 2003]; **Atovaquone Oral Suspension,** *USP 26* page 189 and page 3082 of the *Second Supplement;* **Methenamine Elixir,** *USP 26* page 1182; **Methenamine Oral Solution,** *USP 26* page 1183; **Methenamine Mandelate for Oral Solution,** *USP 26* page 1184; **Methenamine Mandelate Oral Suspension,** *USP 26* page 1185; **Nalidixic Acid Oral Suspension,** *USP 26* page 1265; **Nitrofurantoin Oral Suspension,** *USP 26* page 1316; **Potassium Iodide Oral Solution,** *USP 26* page 1514; **Pyrantel Pamoate Oral Suspension,** *USP 26* page 1595; **Pyrvinium Pamoate Oral Suspension,** *USP 26* page 1603; **Sulfamethizole Oral Suspension,** *USP 26* page 1736; **Sulfamethoxazole Oral Suspension,** *USP 26* page 1737; **Sulfamethoxazole and Trimethoprim Oral Suspension,** *USP 26* page 1739 and page 670 of *PF* 29(3) [May–June 2003]; **Sulfisoxazole Acetyl Oral Suspension,** *USP 26* page 1746; **Thiabendazole Oral Suspension,** *USP 26* page 1811; **Trisulfapyrimidines Oral Suspension,** *USP 26* page 1901; **Zidovudine Oral Solution,** *USP 26* page 1952. It is proposed to improve the standards in monographs for a number of *Oral Solutions* and *Oral Suspensions,* as well as powders *for Oral Solution* and *for Oral Suspension*. It is proposed to add requirements for *Uniformity of dosage units* ⟨905⟩ to apply to single-unit containers, and *Deliverable volume* ⟨698⟩ to apply to multiple-unit containers.

(PA7b: B. Davani) RTS—40396-1

Change to read:

Packaging and storage—Preserve in tight containers. ~~, and store at controlled room temperature.~~

■Store between 15° and 25°. Protect from light.■1S (*USP27*)

In-Process Revision

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Adenosine, *USP 26* page 51 and page 2940 of the *First Supplement;* **Diatrizoate Meglumine,** *USP 26* page 582; **Diatrizoate Sodium,** *USP 26* page 585; **Diatrizoic Acid,** *USP 26* page 586; **Gadodiamide,** *USP 26* page 839; **Gadoteridol,** *USP 26* page 843; **Inulin,** *USP 26* page 980; **Iodipamide,** *USP 26* page 990; **Iodixanol,** *USP 26* page 991; **Iohexol,** *USP 26* page 996; **Iopamidol,** *USP 26* page 998; **Iophendylate,** *USP 26* page 1000; **Iothalamic Acid,** *USP 26* page 1005; **Ioversol,** *USP 26* page 1006; **Ioxaglic Acid,** *USP 26* page 1008; **Ioxalin,** *USP 26* page 1008; **Mangafodipir Trisodium,** *USP 26* page 1121; **Mebrofenin,** *USP 26* page 1133; **Propyliodone,** *USP 26* page 1584. Revisions are proposed to establish consistency with the system of *Labeling* established in 1993 by the USP Drug Nomenclature Committee (see page 5618 of *PF* 19(4) [July–Aug. 1993]). Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms, a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that where the label states that it is sterile, it must meet the requirements of the *Sterility Tests* ⟨71⟩ and of the test for *Bacterial Endotoxins* ⟨85⟩. In addition where the label states that it must be subjected to further processing during the preparation of injectable dosage forms, it must meet the requirements of the test for *Bacterial Endotoxins* ⟨85⟩. In some monographs it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(RMI: A. Wilk; PSD: C. Okeke) RTS—40329-1

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Adenosine RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Alfentanil Hydrochloride, *USP 26* page 61; **Anileridine,** *USP 26* page 155; **Aurothioglucose,** *USP 26* page 194; **Butorphanol Tartrate,** *USP 26* page 294 and page 2946 of the *First Supplement;* **Codeine Phosphate,** *USP 26* page 506; **Fentanyl Citrate,** *USP 26* page 781; **Gold Sodium Thiomalate,** *USP 26* page 871 and page 3101 of the *Second Supplement;* **Hydromorphone Hydrochloride,** *USP 26* page 927; **Ketorolac Tromethamine,** *USP 26* page 1049; **Levorphanol Tartrate,** *USP 26* page 1073; **Meperidine Hydrochloride,** *USP 26* page 1151; **Methadone Hydrochloride,** *USP 26* page 1175; **Methotrimprazine,** *USP 26* page 1191; **Morphine Sulfate,** *USP 26* page 1254; **Nalorphine Hydrochloride,** *USP 26* page 1266; **Naloxone Hydrochloride,** *USP 26* page 1267; **Oxymorphone Hydrochloride,** *USP 26* page 1376; **Phenylephrine Hydrochloride,** *USP 26* page 1459; **Sufentanil Citrate,** *USP 26* page 1720. Revisions are proposed to establish consistency with the system of *Labeling* established in 1993 by the USP Drug Nomenclature Committee (see *PF* 19(4) [July-Aug. 1993] page 5618). Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that where the label states that it is sterile, it must meet the requirements of the test for *Sterility* ⟨71⟩ and of the test for *Bacterial endotoxins* ⟨85⟩. In addition, where the label states that it must be subjected to further processing during the preparation of injectable dosage forms, it must meet the requirements of the test for *Bacterial endotoxins* ⟨85⟩. In some monographs it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA2: C. Anthony) RTS—40339-1

In-Process Revision

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Alfentanil Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Alteplase, *USP 26* page 69—See briefing under *Acepromazine Maleate.*

(VET: I. DeVeau) RTS—40270-2

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Alteplase is sterile, it meets the requirements for *Sterility* under *Alteplase for Injection.*■2S (*USP27*)

BRIEFING

Alumina, Magnesia, and Calcium Carbonate Tablets, *USP 26,* page 76 and page 2515 of *PF* 27(3) [May–June 2001]. Revisions are proposed by the Expert Committee on Nomenclature and Labeling to change the titles of nine USP monographs for tablets that must be chewed before being swallowed. The revisions are those that are proposed to change the current titles that are in the general form [DRUG(S)] Tablets to the general form [DRUG(S)] Chewable Tablets. The Expert Committee on Nomenclature and Labeling considers that the term "Chewable" appearing prominently in a product name will represent a significant improvement in that the consumer will be provided with the assurance that, along with the labeling statement directing that "tablets must be chewed before being swallowed," the product will be used properly to achieve the benefit of the medication.

This proposed nomenclature revision is not intended for tablets that may (not must) be chewed before being swallowed or that may be swallowed intact.

The revisions are proposed for publication in the *Second Supplement to USP 27–NF 22,* which is to become official August 1, 2004, but with February 1, 2007 designated as the official date for the name changes. Use of the revised names would be permitted as of the August 1, 2004 official date of the *Second Supplement to USP 27–NF 22,* but use of the revised names would not become mandatory until February 1, 2007. The thirty-month postponement of the official date for the name changes is intended to allow for product label changes to be made and for health practitioners and consumers to become familiar with the revised terminology.

(NL: C. Barnstein; W. Paul; PSD: C. Okeke) RTS—40424-1

Alumina, Magnesia, and Calcium Carbonate Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Alumina, Magnesia, and Calcium Carbonate Chewable Tablets**

Change to read:

Packaging and storage—Preserve in ~~well-closed~~

■tight■1S (*USP27*)
containers,

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

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BRIEFING

Alumina, Magnesia, and Calcium Carbonate Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul; PSD: C. Okeke) RTS—40424-1

Add the following:

■Alumina, Magnesia, and Calcium Carbonate Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Alumina, Magnesia, and Calcium Carbonate Tablets)

» Alumina, Magnesia, and Calcium Carbonate Chewable Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of aluminum hydroxide [$Al(OH)_3$], magnesium hydroxide [$Mg(OH)_2$], and calcium carbonate ($CaCO_3$).

Packaging and storage—Preserve in ~~well closed~~ tight containers, and store at controlled room temperature.

Labeling—Label the Chewable Tablets to indicate that they are to be chewed before being swallowed. Chewable Tablets prepared with the use of *Dried Aluminum Hydroxide* may be labeled to state the aluminum hydroxide content in terms of the equivalent amount of dried aluminum hydroxide gel, on the basis that each mg of dried gel is equivalent to 0.765 mg of $Al(OH)_3$.

Identification—To a 3-g portion of finely powdered Chewable Tablets add 25 mL of water and 25 mL of 2 N sulfuric acid, stir, and heat on a steam bath for 10 minutes. Cool, add 50 mL of alcohol, and stir: the mixture so obtained responds to *Identification* tests *A*, *B*, and *C* under *Alumina, Magnesia, and Calcium Carbonate Oral Suspension*, beginning under *Identification* test *A* with "place in an ice bath for 30 minutes."

Disintegration ⟨701⟩: 45 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements for *Weight Variation* with respect to alumina, to magnesia, and to calcium carbonate.

Acid-neutralizing capacity ⟨301⟩—Not less than 5 mEq of acid is consumed by the minimum single dose recommended in the labeling, and not less than the number of mEq calculated by the formula:

$$0.55(0.0385A) + 0.8(0.0343M) + 0.9(0.02C),$$

in which 0.0385, 0.0343, and 0.02 are the theoretical acid-neutralizing capacities, in mEq, of $Al(OH)_3$, $Mg(OH)_2$, and $CaCO_3$, respectively, and *A*, *M*, and *C* are the respective quantities, in mg, of $Al(OH)_3$, $Mg(OH)_2$, and $CaCO_3$ in the specimen tested, based on the labeled quantities.

Assay for aluminum hydroxide—

Edetate disodium titrant—Prepare as directed in the *Assay for aluminum hydroxide* under *Alumina, Magnesia, and Calcium Carbonate Oral Suspension*.

Assay preparation—Weigh and finely powder not fewer than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 600 mg of aluminum hydroxide, to a beaker, add 20 mL of water, and slowly add 40 mL of 3 N hydrochloric acid, with mixing. Heat the mixture to boiling, cool, and filter into a 200-mL volumetric flask. Wash the beaker with water, adding the washings to the filter. Add water to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay for aluminum hydroxide* under *Alumina, Magnesia, and Calcium Carbonate Oral Suspension*. Each mL of 0.05 M *Edetate disodium titrant* is equivalent to 3.900 mg of $Al(OH)_3$.

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Assay for magnesium hydroxide—

Edetate disodium titrant and *Assay preparation*—Prepare as directed in the *Assay for aluminum hydroxide*.

Procedure—Proceed as directed for *Procedure* in the *Assay for magnesium hydroxide* under *Alumina, Magnesia, and Calcium Carbonate Oral Suspension*. Each mL of 0.05 M *Edetate disodium titrant* is equivalent to 2.916 mg of $Mg(OH)_2$.

Assay for calcium carbonate—

Edetate disodium titrant and *Assay preparation*—Prepare as directed in the *Assay for aluminum hydroxide*.

Procedure—Proceed as directed for *Procedure* in the *Assay for calcium carbonate* under *Alumina, Magnesia, and Calcium Carbonate Oral Suspension*. Each mL of 0.05 M *Edetate disodium titrant* is equivalent to 5.004 mg of $CaCO_3$. ■2S (*USP27*)

(Official February 1, 2007)

BRIEFING

Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets, *USP 26* page 76 and page 2516 of *PF* 27(3) [May–June 2001]. It is proposed to change the title of this monograph to *Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; L. Paul; PSD: C. Okeke) RTS—40425-1

Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets**

Change to read:

Packaging and storage—Preserve in ~~well closed~~ ■tight■1S (*USP27*) containers, ■and store at controlled room temperature.■1S (*USP27*)

BRIEFING

Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; L. Paul; PSD: C. Okeke) RTS—40425-1

Add the following:

■Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets)

» Alumina, Magnesia, Calcium Carbonate, and Simethicone Chewable Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of aluminum hydroxide [$Al(OH)_3$], magnesium hydroxide [$Mg(OH)_2$], and calcium carbonate ($CaCO_3$), and an amount of polydimethylsiloxane ([$–(CH_3)_2SiO–]_n$) that is not less than 85.0 percent and not more than 115.0 percent of the labeled amount of simethicone.

Packaging and storage—Preserve in tight containers, and store at controlled room temperature.

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Labeling—The labeling indicates that the Chewable Tablets are to be chewed before swallowing. Label the Chewable Tablets to state the sodium content, if it is greater than 5 mg per Chewable Tablet.

USP Reference standards ⟨11⟩—*USP Polydimethylsiloxane RS.*

Identification—

A: Cut a Chewable Tablet into pieces, add 50 mL of 1 N sulfuric acid, stir until the pieces disintegrate, and heat on a steam bath for 10 minutes. Cool, add 50 mL of alcohol, and stir. The mixture so obtained responds to *Identification* tests *A*, *B*, and *C* under *Alumina, Magnesia, and Calcium Carbonate Oral Suspension,* beginning under *Identification* test *A* with "place in an ice bath for 30 minutes."

B: *Infrared Absorption* ⟨197S⟩—

Cell: 0.5 mm.

Solution: prepared as directed in the *Assay for polydimethylsiloxane.*

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 200 per g, the total combined molds and yeasts count does not exceed 200 per g, and the Chewable Tablets meet the requirements of the test for the absence of *Salmonella* species and *Escherichia coli.*

Uniformity of dosage units ⟨905⟩: meet the requirements for *Weight Variation* with respect to aluminum hydroxide, to magnesium hydroxide, and to calcium carbonate.

Acid-neutralizing capacity ⟨301⟩—Dissolve an accurately counted number of Chewable Tablets, equivalent to about 120 mEq of acid-neutralizing capacity, in about 400 mL of water. Transfer the mixture to a 500-mL volumetric flask, dilute with water to volume, and mix. Use 75.0 mL of this solution as the *Test preparation*. Proceed as directed in the section *Procedure for Powders, Effervescent Solids, Suspensions and Other Liquids, Nonchewable Tablets, Chewable Tablets, and Capsules.* The acid consumed by the minimum single dose recommended in the labeling is not less than 5 mEq, and not less than the number of mEq calculated by the formula:

$$0.55(0.0385A) + 0.8(0.0343M) + 0.9(0.02C),$$

in which 0.0385, 0.0343, and 0.02 are the theoretical acid-neutralizing capacities, in mEq, of $Al(OH)_3$, $Mg(OH)_2$, and $CaCO_3$, respectively, and *A*, *M*, and *C* are the quantities, in mg, of $Al(OH)_3$, $Mg(OH)_2$, and $CaCO_3$ in the specimen tested, based on the labeled quantities.

Defoaming activity—

Foaming solution—Dissolve 1 g of octoxynol 9 in 100 mL of 0.3 N hydrochloric acid.

Procedure—[NOTE—For each test, use a clean 250-mL cylindrical glass jar.] Weigh not fewer than 10 Chewable Tablets, cut them into small pieces, and mix. Transfer a portion of mixed Tablet pieces, equivalent to about 20 mg of simethicone, to a clean 250-mL cylindrical glass jar, fitted with a 50-mm cap, containing 100 mL of *Foaming solution* that has been warmed to 37°. After effervescence ceases, proceed as directed for *Procedure* in the *Defoaming activity* test under *Simethicone,* beginning with "Cap the jar." The defoaming activity time does not exceed 45 seconds.

Sodium content—

Potassium chloride solution—Dissolve 3 g of potassium chloride in water in a 100-mL volumetric flask, dilute with water to volume, and mix.

Dilute hydrochloric acid—Prepare by mixing 226 mL of hydrochloric acid with sufficient water to make 1000 mL.

Standard solution—Transfer 2.5420 g of sodium chloride, previously dried at 105° for 2 hours, to a 1000-mL volumetric flask, dissolve in and dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a second 100-mL volumetric flask, dilute with water to volume, and mix. To three

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separate 100-mL volumetric flasks, each containing 10.0 mL of *Potassium chloride solution* and 3.0 mL of *Dilute hydrochloric acid,* add, respectively, 10.0, 20.0, and 30.0 mL of this solution. These solutions contain 1.0, 2.0, and 3.0 µg of sodium (Na) per mL, respectively.

Test solution—Accurately weigh 10 Chewable Tablets, and determine the average weight, *A,* in mg. Cut 4 Chewable Tablets into pieces, combine the pieces, and weigh them. Transfer the combined pieces to a 500-mL volumetric flask, add 150 mL of *Dilute hydrochloric acid,* and swirl gently to disintegrate the pieces. Dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, add 10.0 mL of *Potassium chloride solution,* dilute with water to volume, and mix.

Blank solution—Transfer 3.0 mL of *Dilute hydrochloric acid* and 10.0 mL of *Potassium chloride solution* to a 100-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard solutions* and the *Test solution* at the sodium emission line at 589.0 nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a sodium hollow-cathode lamp and an air–acetylene flame, using the *Blank solution* as the blank. Plot the absorbances of the *Standard solutions* versus concentration, in µg per mL, of sodium, and draw the straight line best fitting the three plotted points. From the graph so obtained, determine the concentration, *C,* in µg per mL, of sodium in the *Test solution.* Calculate the mg of sodium (Na) in each Chewable Tablet taken by the formula:

$$5C(A/W),$$

in which *A* is the average weight, in mg, of each Chewable Tablet and *W* is the weight, in mg, of the portion of Chewable Tablets taken to prepare the *Test solution.* Tablets contain not more than 5 mg of sodium per Chewable Tablet, except when labeled as containing more than 5 mg of sodium per Chewable Tablet, they contain not more than 110% of the labeled amount.

Assay for aluminum hydroxide—

Edetate disodium titrant—Prepare and standardize as directed in the *Assay* under *Ammonium Alum.*

Assay preparation—Transfer an accurately counted number of Chewable Tablets, equivalent to about 665 mg of aluminum hydroxide, to a suitable beaker. Add 15 mL of hydrochloric acid, and swirl to dissolve the Tablets. Add 80 mL of water, and filter into a 200-mL volumetric flask. Wash the filter with water into the flask, add water to volume, and mix.

Procedure—Pipet 20 mL of *Assay preparation* into a 250-mL beaker, then add, in the order named and with continuous stirring, 25.0 mL of *Edetate disodium titrant* and 20 mL of acetic acid–ammonium acetate buffer TS, and heat near the boiling temperature for 5 minutes. Cool, add 50 mL of alcohol and 2 mL of dithizone TS, and mix. Titrate with 0.05 M zinc sulfate VS until the color changes from green-violet to rose-pink. Perform a blank determination, substituting 20 mL of water for the *Assay preparation,* and making any necessary correction. Each mL of *0.05 M Edetate disodium titrant* consumed is equivalent to 3.900 mg of $Al(OH)_3$.

Assay for magnesium hydroxide—

Lanthanum chloride solution—Transfer 17.6 g of lanthanum chloride to a 200-mL volumetric flask, add 100 mL of water, and carefully add 50 mL of hydrochloric acid. Mix, and allow to cool. Dilute with water to volume, and mix.

Dilute hydrochloric acid—Prepare by mixing 226 mL of hydrochloric acid with sufficient water to make 1000 mL.

Potassium chloride solution—Dissolve 3 g of potassium chloride in water in a 100-mL volumetric flask, dilute with water to volume, and mix.

Magnesium stock solution—Transfer 1.000 g of magnesium metal to a 1000-mL volumetric flask containing 10 mL of water, slowly add 10 mL of hydrochloric acid, and swirl to dissolve the metal. Dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. This solution contains 20 µg of magnesium (Mg) per mL.

Standard preparations—To three separate 100-mL volumetric flasks each containing 5.0 mL of *Lanthanum chloride solution,* add 1.0, 2.0, and 3.0 mL, respectively, of the *Magnesium stock solution.* Dilute each with water to volume, and mix. These solutions contain 0.1, 0.2, and 0.3 µg of magnesium (Mg) per mL, respectively.

Assay preparation—Transfer an accurately counted number of Chewable Tablets, equivalent to about 250 mg of magnesium hydroxide (100 mg of magnesium), to a 1000-mL volumetric flask. Add 500 mL of *Dilute hydrochloric acid,* and swirl to disintegrate the Tablets. Add 100.0 mL of *Potassium chloride solution,* dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a second 100-mL volumetric flask, add 5.0 mL of *Lanthanum chloride solution,* dilute with water to volume, and mix.

Blank—Add 50 mL of *Dilute hydrochloric acid* and 10.0 mL of *Potassium chloride solution* to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a second 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 2.0 mL of this solution to a third 100-mL volumetric flask, add 5.0 mL of *Lanthanum chloride solution,* dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparations* and the *Assay preparation* at the magnesium emission line at 285.2 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a magnesium hollow-cathode lamp and an air–acetylene flame, using the *Blank* to set the instrument. Plot the absorbances of the *Standard preparations* versus concentration, in µg per mL, of magnesium, and draw the straight line best fitting the three plotted points. From the graph so obtained, determine the concentration, *C*, in µg per mL, of magnesium in the *Assay preparation.* Calculate the quantity, in mg, of magnesium hydroxide [$Mg(OH)_2$] in each Chewable Tablet taken by the formula:

$$(58.34/24.305)(500C/N),$$

in which 58.34 is the molecular weight of magnesium hydroxide; 24.305 is the atomic weight of magnesium; and *N* is the number of Chewable Tablets taken to prepare the *Assay preparation.*

Assay for calcium carbonate—

Assay preparation—Prepare as directed in the *Assay for aluminum hydroxide.*

Procedure—Pipet a volume of the *Assay preparation,* equivalent to about 50 mg of calcium carbonate, into a 400-mL beaker, and add 200 mL of water, a volume of sodium hydroxide solution (1 in 2) equivalent to the volume of the *Assay preparation* taken, and 250 mg of hydroxy naphthol blue. Stir with a magnetic stirrer, and titrate immediately with 0.05 M edetate disodium VS until the solution is distinctly blue. Perform a blank determination, substituting a volume of water equivalent to the volume of the *Assay preparation* taken, and make any necessary correction. Each mL of 0.05 M edetate disodium is equivalent to 5.004 mg of $CaCO_3$.

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Assay for polydimethylsiloxane—

Dilute hydrochloric acid—Prepare by mixing 400 mL of hydrochloric acid with sufficient water to make 1000 mL.

Standard preparation—Transfer about 60 mg of USP Polydimethylsiloxane RS, accurately weighed, to a separator, add 30.0 mL of chloroform and 60 mL of *Dilute hydrochloric acid*, shake for 30 seconds, and allow the phases to separate. Remove about 10 mL of the lower, organic layer to a screw-capped, 15-mL test tube containing 0.5 g of anhydrous sodium sulfate. Close the tube with a screw-cap having an inert liner, agitate vigorously, and centrifuge the mixture until a clear supernatant is obtained (*Standard preparation*).

Assay preparation—Weigh and finely powder not fewer than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 60 mg of simethicone, to a suitable screw-capped bottle, add 30.0 mL of chloroform and 60 mL of *Dilute hydrochloric acid*, and allow to stand, with frequent shaking, until the Chewable Tablets are dissolved. Transfer the contents of the bottle to a separator, shake, and allow the phases to separate. Remove about 10 mL of the lower, organic layer to a screw-capped, 15-mL test tube containing 0.5 g of anhydrous sodium sulfate. Close the tube with a screw-cap having an inert liner, agitate vigorously, and centrifuge the mixture until a clear supernatant is obtained (*Assay preparation*).

Blank—Place 30.0 mL of chloroform and 60 mL of *Dilute hydrochloric acid* in a separator, shake for 30 seconds, and allow the phases to separate. Remove about 10 mL of the lower, organic layer to a screw-capped, 15-mL test tube containing 0.5 g of anhydrous sodium sulfate. Close the tube with a screw-cap having an inert liner, agitate vigorously, and centrifuge the mixture until a clear supernatant is obtained (*Blank*).

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* in 0.5-mm cells at the wavelength of maximum absorbance at about 7.9 µm, with a suitable IR spectrophotometer, using the *Blank* to set the instrument. Calculate the quantity, in mg, of $[–(CH_3)_2SiO–]_n$ in each Chewable Tablet taken by the formula:

$$(W/N)(A_U / A_S),$$

in which W is the weight, in mg, of USP Polydimethylsiloxane RS used in preparing the *Standard preparation; N* is the number of Chewable Tablets taken to prepare the *Assay preparation;* and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

(Official February 1, 2007)

BRIEFING

Alumina, Magnesia, and Simethicone Tablets, *USP 26* page 79. It is proposed to change the title of this monograph to *Alumina, Magnesia, and Simethicone Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40426-1

Alumina, Magnesia, and Simethicone Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Alumina, Magnesia, and Simethicone Chewable Tablets**

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BRIEFING

Alumina, Magnesia, and Simethicone Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40426-1

Add the following:

■Alumina, Magnesia, and Simethicone Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Alumina, Magnesia, and Simethicone Tablets)

» Alumina, Magnesia, and Simethicone Chewable Tablets contain the equivalent of not less than 90.0 percent and not more than 115.0 percent of the labeled amounts of aluminum hydroxide [$Al(OH)_3$] and magnesium hydroxide [$Mg(OH)_2$], and an amount of polydimethylsiloxane [$–(CH_3)_2SiO–]_n$ that is not less than 85.0 percent and not more than 115.0 percent of the labeled amount of simethicone.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label the Chewable Tablets to indicate that they are to be chewed before being swallowed. Label the Chewable Tablets to state the sodium content if it is greater than 5 mg per Tablet. The Chewable Tablets may be labeled to state the aluminum hydroxide content in terms of the equivalent amount of dried aluminum hydroxide gel, on the basis that each mg of dried gel is equivalent to 0.765 mg of $Al(OH)_3$.

USP Reference standards ⟨11⟩—*USP Polydimethylsiloxane RS.*

Identification—

A: *Infrared Absorption* ⟨197S⟩—

Cell: 0.5 mm.

Solution: prepared as directed in the *Assay for polydimethylsiloxane.*

B: To a portion of finely powdered Chewable Tablets, equivalent to about 600 mg of magnesium hydroxide, add 25 mL of 3 N hydrochloric acid and 25 mL of water, and mix. Boil gently for 2 minutes. Allow to cool, and filter. Add 5 drops of methyl red TS, heat to boiling, and add 6 N ammonium hydroxide until the color of the solution just turns to deep yellow. Continue boiling for 2 minutes, and filter: the filtrate so obtained responds to the tests for *Magnesium* ⟨191⟩.

C: Wash the precipitate obtained in *Identification* test *B* with a hot solution of ammonium chloride (1 in 50), and dissolve the precipitate in hydrochloric acid: the solution so obtained responds to *Identification* test *C* under *Alumina, Magnesia, and Simethicone Oral Suspension.*

Uniformity of dosage units ⟨905⟩: meet the requirements for *Weight Variation* with respect to aluminum hydroxide and to magnesium hydroxide.

Acid-neutralizing capacity ⟨301⟩—The acid consumed by the minimum single dose recommended in the labeling is not less than 5 mEq, and not less than the number of mEq calculated by the formula:

$$0.55(0.0385A) + 0.8(0.0343M),$$

in which 0.0385 and 0.0343 are the theoretical acid-neutralizing capacities, in mEq, of $Al(OH)_3$ and $Mg(OH)_2$, respectively, and A and M are the quantities, in mg, of $Al(OH)_3$ and $Mg(OH)_2$ in the specimen tested, based on the labeled quantities.

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Defoaming activity—

Foaming solution—Dissolve 500 µg of FD&C Blue No. 1 and 1 g of octoxynol 9 in 100 mL of 0.1 N hydrochloric acid.

Procedure—[NOTE—For each test, employ a clean, unused, 250-mL glass jar.] Transfer a quantity of finely powdered Chewable Tablets, passed completely through an 80-mesh sieve, equivalent to 20 mg of simethicone, to a clean, unused, cylindrical 250-mL glass jar, fitted with a 50-mm cap, containing 100 mL of *Foaming solution* that has been warmed to 37°. Proceed as directed for *Procedure* in the test for *Defoaming activity* under *Simethicone,* beginning with "Cap the jar." The defoaming activity time does not exceed 45 seconds.

Sodium content—

Potassium chloride solution, Sodium chloride stock solution, and *Standard preparations*—Prepare as directed in the test for *Sodium content* under *Alumina, Magnesia, and Simethicone Oral Suspension.*

Test preparation—Weigh and finely powder not less than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to the average weight of 1 Chewable Tablet, to a 100-mL volumetric flask. Add 50 mL of 1 N hydrochloric acid, boil for 15 minutes, cool to room temperature, dilute with water to volume, and mix. Filter, discarding the first few mL of the filtrate. Transfer 5.0 mL of the filtrate to a 100-mL volumetric flask containing 10.0 mL of *Potassium chloride solution,* dilute with water to volume, and mix.

Procedure—Proceed as directed in the test for *Sodium content* under *Alumina, Magnesia, and Simethicone Oral Suspension.* Calculate the quantity, in mg, of sodium per Chewable Tablet taken by the formula:

$$2C.$$

Assay for aluminum hydroxide—

Edetate disodium titrant—Prepare and standardize as directed in the *Assay* under *Ammonium Alum.*

Assay preparation—Weigh and finely powder not less than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 800 mg of aluminum hydroxide, to a 150-mL beaker, add 20 mL of water, stir, and slowly add 30 mL of 3 N hydrochloric acid. Heat gently, if necessary, to aid solution, cool to room temperature, and filter into a 200-mL volumetric flask. Wash the filter with water into the flask, add water to volume, and mix.

Procedure—Proceed as directed for *Procedure* in the *Assay for aluminum hydroxide* under *Alumina, Magnesia, and Simethicone Oral Suspension.*

Assay for magnesium hydroxide—

Assay preparation—Prepare as directed in the *Assay for aluminum hydroxide*.

Procedure—Proceed as directed for *Procedure* in the *Assay for magnesium hydroxide* under *Alumina, Magnesia, and Simethicone Oral Suspension.*

Assay for polydimethylsiloxane—Weigh and finely powder not less than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 33 mg of simethicone, to a suitable round, narrow-mouth, screw-capped, 120-mL bottle, add 40 mL of 0.1 N sodium hydroxide, and swirl to disperse. Add 20.0 mL of toluene, close the bottle securely with a cap having an inert liner, and shake for 30 minutes, accurately timed, on a reciprocating shaker (e.g., about 200 oscillations per minute and a stroke of 38 ± 2 mm). Transfer the mixture to a 125-mL separator, and allow to separate. Remove the upper, organic layer to a screw-capped, centrifuge tube containing about 2 g of anhydrous sodium sulfate. Close the tube with a screw-cap having an inert liner, agitate vigorously, and centrifuge the mixture until a clear supernatant (*Assay preparation*) is

obtained. Similarly prepare a *Standard preparation*, using about 33 mg of USP Polydimethylsiloxane RS, accurately weighed. Prepare a blank by mixing 10 mL of toluene with about 1 g of anhydrous sodium sulfate and centrifuging to obtain a clear supernatant. Concomitantly determine the absorbances of the solutions in 0.5-mm cells at the wavelength of maximum absorbance at about 7.9 µm (1265.8 cm^{-1}), with a suitable IR spectrophotometer, using the blank to set the instrument. Calculate the quantity, in mg, of $[–(CH_3)_2SiO–]_n$ in the portion of Chewable Tablets taken by the formula:

$$(W)(A_U / A_S),$$

in which W is the weight, in mg, of USP Polydimethylsiloxane RS used to prepare the *Standard preparation,* and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

(Official February 1, 2007)

Change to read:

USP Reference standards ⟨11⟩—*USP Aminopentamide Sulfate RS*.

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

Change to read:

Assay—Dissolve about 500 mg of Aminopentamide Sulfate, accurately weighed, in 100 mL of dimethylformamide in a suitable container. Add 5 drops of thymol blue TS, and titrate with 0.1 N lithium methoxide VS

■in benzene■2S (*USP27*)
to a deep blue endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N lithium methoxide is equivalent to 19.72 mg of $C_{19}H_{24}N_2O \cdot H_2SO_4$.

BRIEFING

Aminopentamide Sulfate, *USP 26* page 123 and page 1414 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Acepromazine Maleate*.

(VET: I. DeVeau) RTS—40270-3

Change to read:

Labeling—Label it to indicate that it is for veterinary use only.

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

BRIEFING

Amitriptyline Hydrochloride, *USP 26* page 132; **Amobarbital Sodium,** *USP 26* page 136; **Atracurium Besylate,** *USP 26* page 190; **Atropine Sulfate,** *USP 26* page 192; **Baclofen,** *USP 26* page 208; **Benztropine Mesylate,** *USP 26* page 228; **Bethanechol Chloride,** *USP 26* page 244 and page 52 of *PF* 29(1) [Jan.–Feb. 2003]; **Biperiden,** *USP 26* page 249; **Caffeine,** *USP 26* page 295; **Chlordiazepoxide Hydrochloride,** *USP 26* page 417; **Chlorpromazine Hydrochloride,** *USP 26* page 434; **Diazepam,** *USP 26* page 587; **Dihydroergotamine Mesylate,** *USP 26* page 617 and page 1463 of *PF* 29(5) [Sept.–Oct. 2003]; **Doxapram Hydrochloride,** *USP 26* page 662; **Droperidol,** *USP 26* page 674 and page 1473 of *PF* 29(5) [Sept.–Oct. 2003]; **Ergotamine Tatrtrate,** *USP 26* page 723; **Fluphenazine Decanoate,** *USP 26* page 820; **Fluphenazine Enanthate,** *USP 26* page 821; **Fluphenazine Hydrochloride,** *USP 26* page 821; **Fosphenytoin Sodium,** *USP 26* page 833 and page 1492 of *PF* 29(5) [Sept.–Oct. 2003]; **Haloperidol,** *USP 26* page 893 and page 1504 of *PF* 29(5) [Sept.–Oct. 2003]; **Hydroxyzine Hydrochloride,** *USP 26* page 935; **Imipramine Hydrochloride,** *USP 26* page 956; **Lorazepam,** *USP 26* page 1096; **Magnesium Sulfate,** *USP 26* page 1118; **Mesoridazine Besylate,** *USP 26* page 1166; **Methocarbamol,** *USP 26* page 1187; **Neostigmine Methylsulfate,** *USP 26* page 1303; **Ondansetron Hydrochloride,** *USP 26* page 1351 and page 1548 of *PF* 29(5) [Sept.–Oct. 2003]; **Orphenadrine Citrate,** *USP 26* page

1354 and page 94 of *PF* 29(1) [Jan.–Feb. 2003]; **Pentobarbital,** *USP 26* page 1429 and page 655 of *PF* 29(3) [May–June 2003]; **Pentobarbital Sodium,** *USP 26* page 1431and page 1558 of *PF* 29(5) [Sept.–Oct. 2003]; **Perphenazine,** *USP 26* page 1438; **Phenobarbital,** *USP 26* page 1448; **Phenobarbital Sodium,** *USP 26* page 1449; **Phenytoin Sodium,** *USP 26* page 1467; **Physostigmine Salicylate,** *USP 26* page 1473; **Pyridostigmine Bromide,** *USP 26* page 1597; **Secobarbital Sodium,** *USP 26* page 1671; **Thiothixene Hydrochloride,** *USP 26* page 1828; **Trifluoperazine Hydrochloride,** *USP 26* page 1880; **Triflupromazine Hydrochloride,** *USP 26* page 1884; **Tubocurarine Chloride,** *USP 26* page 1907. Revisions are proposed to establish consistency with the system of Labeling established in 1993 by the USP Drug Nomenclature Committee (see *PF* 19(4) [July-Aug. 1993] page 5618). Specifically, it is now proposed to include in each monograph of drug substances (active pharmaceutical ingredients) intended for use in preparing injectable dosage forms a statement that it is sterile or must be subjected to further processing during the preparation of injectable dosage forms. A new section on *Other requirements* is proposed stating that where the label states that it is sterile it must meet the requirements of the *Sterility Tests* ⟨71⟩ and of the test for *Bacterial endotoxins* ⟨85⟩. In addition, where the label states that it must be subjected to further processing during the preparation of injectable dosage forms, it must meet the requirements of the test for *Bacterial endotoxins* ⟨85⟩. In some monographs it is proposed to revise the section on *Packaging and storage* to indicate appropriate storage temperatures.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-1

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Amitriptyline Hydrochloride is sterile, it meets the requirements for *Sterility* and *Pyrogen* under *Amitriptyline Hydrochloride Injection.*■2S (*USP27*)

BRIEFING

Ferric Ammonium Citrate for Oral Solution, *USP 26* page 135; **Cyanocobalamin Co 57 Oral Solution,** *USP 26* page 502 and page 397 of *PF* 29(2) [Mar.–Apr. 2003]; **Ferumoxsil Oral Suspension,** *USP 26* page 790; **Manganese Chloride for Oral Solution,** *USP 26* page 1124. It is proposed to improve the standards in a number of oral solution, oral suspension, ''for oral solution'' and ''for oral suspension'' monographs by adding requirements for *Uniformity of dosage units* ⟨905⟩ for single-unit containers and requirements for *Deliverable volume* ⟨698⟩ for multiple-unit containers.

(RMI: A. Wilk) RTS—40369-1

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS:

meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS:

meets the requirements.■2S (*USP27*)

BRIEFING

Amobarbital Sodium, *USP 26* page 136—See briefing under *Amitriptyline Hydrochloride.*

(PSD: C. Okeke) RTS—40364-2

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Anileridine, *USP 26* page 155—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40340-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Atovaquone Oral Suspension, *USP 26* page 189 and page 3082 of the *Second Supplement*—See briefing under *Acyclovir Oral Suspension.*

(PA7b: B. Davani) RTS—40401-1

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Change to read:

Deliverable volume ⟨698⟩—

■FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: ■2S (*USP27*)
meets the requirements.

BRIEFING

Atracurium Besylate, *USP 26* page 190—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado) RTS—40364-3

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Atracurium Besylate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Atropine Sulfate, *USP 26* page 192—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-4

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Atropine Sulfate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Aurothioglucose, *USP 26* page 194—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40341-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Aurothioglucose is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Azaperone, *USP 26* page 195—See briefing under *Acepromazine Maleate.*

(VET: I. DeVeau; PSD: C. Okeke) RTS—40270-4

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate that it is for veterinary use only.

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

Add the following:

■**Other requirements—**Where the label states that Azaperone is sterile, it meets the requirements for *Sterility* under *Azaperone Injection.*■2S (*USP27*)

BRIEFING

Baclofen, *USP 26* page 208—See briefing under *Amitriptyline Hydrochloride.*

(PSD: C. Okeke) RTS—40364-5

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Benztropine Mesylate, *USP 26* page 228—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-6

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Benztropine Mesylate RS.* ■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Bethanechol Chloride, *USP 26* page 244 and page 52 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-7

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

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Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Bethanechol Chloride RS.* ■*USP Endotoxin RS.*■2S *(USP27)*

Add the following:

▲**Related compounds—**

Buffer solution—Transfer about 0.48 g of methanesulfonic acid to a 1000-mL volumetric flask. Dissolve in and dilute with water to volume.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (95:5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in *Mobile phase* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1 µg of USP Bethanechol Chloride RS per mL.

Test solution—Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a 250-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

System suitability solution—Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a 250-mL volumetric flask. Add 10 mL of 0.1 N sodium hydroxide, and allow to stand for about 15 minutes. Add 10 mL of 0.1 N hydrochloric acid. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatography system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector and a 3.9- × 150-mm column containing packing L60. The flow rate is about 1.0 mL per minute. The detector and column temperature are maintained at 35° and 30°, respectively. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention time is about 0.9 for 2-hydroxypropyltrimethyl ammonium chloride and 1.0 for bethanechol; the resolution, *R,* between 2-hydroxypropyltrimethyl ammonium chloride and bethanechol is not less than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10.0% for bethanechol chloride.

Procedure—Separately inject equal volumes (about 50 µL) of the *Mobile phase, Standard solution,* and *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for all the peaks. Calculate the percentage of each impurity in the portion of Bethanechol Chloride taken by the formula:

$$2500C(F/W)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Bethanechol Chloride RS in the *Standard solution; F* is the relative response factor and is equal to 0.79 for 2-hydroxypropyltrimethyl ammonium and 1.0 for any other impurity; r_i is the peak response for any impurity in the *Test solution;* r_S is the peak response of USP Bethanechol Chloride RS in the *Standard solution;* and W is the weight, in mg, of Bethanechol Chloride taken to prepare the *Test solution.* Not more than 1.0% of 2-hydroxypropyltrimethyl ammonium is found, not more than 0.1% of any other impurity is found, and the sum of all the impurities is not more than 1.5%.▲*USP27*

Add the following:

■**Other requirements—**Where the label states that Bethanechol Chloride is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Bethanechol Chloride*

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Injection. Where the label states that Bethanechol Chloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Bethanechol Chloride Injection.* ■2S (*USP27*)

Change to read:

Assay— ~~Dissolve about 500 mg of Bethanechol Chloride, accurately weighed, in a mixture of 10 mL of glacial acetic acid and 10 mL of mercuric acetate TS. Add 2 drops of crystal violet TS, and titrate with 0.1 N perchloric acid VS. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 19.67 mg of $C_7H_{17}ClN_2O_2$.~~

▲*Buffer solution*—Transfer about 29 mg of edetate disodium to a 1000-mL volumetric flask, and dissolve in 500 mL of water. Add 300 µL of nitric acid to the volumetric flask, and dilute with water to volume. Filter through 0.45-µm nylon membrane filter.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (95:5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a 250-mL volumetric flask. Add 10 mL of 0.1 N sodium hydroxide, and allow to stand for about 15 minutes. Add 10 mL of 0.1 N hydrochloric acid. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard preparation—Dissolve an accurately weighed quantity of USP Bethanechol Chloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg of USP Bethanechol Chloride RS per mL.

Assay preparation—Transfer about 25 mg of Bethanechol Chloride, accurately weighed, to a 250-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a conductivity detector and a 3.9- × 150-mm column containing packing L60. The flow rate is about 1.0 mL per minute. The detector and column temperature are maintained at 35° and 30°, respectively. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for 2-hydroxypropyltrimethyl ammonium chloride and 1.0 for bethanechol, and the resolution, *R,* between 2-hydroxypropyltrimethyl ammonium chloride and Bethanechol is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 3.5; and the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the quantity, in mg, of $C_7H_{17}ClN_2O_2$ in the portion of Bethanechol Chloride taken by the formula:

$$250C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Bethanechol Chloride RS in the *Standard preparation;* and r_U and r_S are the bethanechol chloride peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ▲*USP27*

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BRIEFING

Biperiden, *USP 26* page 249—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-8

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Biperiden RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Biperiden is sterile, it meets the requirements for sterility under *Sterility Tests* ⟨71⟩ and for *Bacterial Endotoxins* ⟨85⟩, the limit being not more than 107 USP Endotoxin Units per mg of biperiden. Where the label states that Biperiden must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* specified above.■2S (*USP27*)

BRIEFING

Butorphanol Tartrate, *USP 26* page 294 and page 2946 of the *First Supplement*—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40342-1

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Butorphanol Tartrate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Caffeine, *USP 26* page 295—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-9

Change to read:

Packaging and storage—Preserve hydrous Caffeine in tight containers. Preserve anhydrous Caffeine in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Caffeine RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Calcium Carbonate and Magnesia Tablets, *USP 26* page 302. It is proposed to change the title of this monograph to *Calcium Carbonate and Magnesia Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40427-1

Calcium Carbonate and Magnesia Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Calcium Carbonate and Magnesia Chewable Tablets**

BRIEFING

Calcium Carbonate and Magnesia Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40427-1

Add the following:

■Calcium Carbonate and Magnesia Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Calcium Carbonate and Magnesia Tablets)

» Calcium Carbonate and Magnesia Chewable Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of calcium carbonate ($CaCO_3$) and not less than 90.0 percent and not more than 115.0 percent of the labeled amount of magnesium hydroxide [$Mg(OH)_2$].

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Packaging and storage—Preserve in well-closed containers.

Labeling—Label the Chewable Tablets to indicate that they are to be chewed before being swallowed.

Identification—

A: The addition of 3 N hydrochloric acid to the Chewable Tablets produces effervescence, and the resulting solution, after being boiled to expel carbon dioxide and neutralized with 6 N ammonium hydroxide, meets the requirements of the tests for *Calcium* ⟨191⟩.

B: Heat 2 Chewable Tablets in 20 mL of 1 N sulfuric acid. Cool, add 20 mL of alcohol, mix, and allow to stand for 30 minutes. Filter this solution, and add 2 mL of 1 N hydrochloric acid to the filtrate: this solution meets the requirements of the tests for *Magnesium* ⟨191⟩.

Uniformity of dosage units ⟨905⟩: meet the requirements for *Weight Variation* with respect to calcium carbonate and to magnesia.

Acid-neutralizing capacity ⟨301⟩—Not less than 5 mEq of acid is consumed by the minimum single dose recommended in the labeling, and not less than the number of mEq calculated by the formula:

$$0.8(0.0343M) + 0.9(0.02C),$$

in which 0.0343 and 0.02 are the theoretical acid-neutralizing capacities, in mEq, of $Mg(OH)_2$ and $CaCO_3$, respectively; and M and C are the respective quantities, in mg, of $Mg(OH)_2$ and $CaCO_3$ in the specimen tested, based on the labeled quantities.

Assay for calcium carbonate—Weigh and finely powder not fewer than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 400 mg of calcium carbonate, to a beaker with 25 mL of water, and add 40 mL of 1 N hydrochloric acid. Heat on a steam bath for 30 minutes, allow to cool, transfer to a 100-mL volumetric flask with the aid of water, dilute with water to volume, mix, and filter. Transfer 20.0 mL of the filtrate to a suitable container, dilute with water to 100 mL, add 30 mL of 1 N sodium hydroxide, 5 mL of triethanolamine, and 100 mg of hydroxy naphthol blue, and titrate with 0.05 M edetate disodium VS until the solution is deep blue in color. Each mL of 0.05 M edetate disodium is equivalent to 5.004 mg of calcium carbonate ($CaCO_3$).

Assay for magnesium hydroxide—Transfer an accurately measured portion of the filtrate remaining from the *Assay for calcium carbonate,* equivalent to about 120 mg of calcium carbonate and magnesium hydroxide combined, to a suitable container, dilute with water to 100 mL, add 10 mL of ammonia–ammonium chloride buffer TS, 5 mL of triethanolamine, and 0.3 mL of eriochrome black TS, and titrate with 0.05 M edetate disodium VS to a blue endpoint. The volume, in mL, of 0.05 M edetate disodium consumed, less the volume of 0.05 M edetate disodium corresponding to the content of calcium carbonate in the volume, in mL, of the filtrate taken, represents the volume, in mL, of 0.05 M edetate disodium equivalent to the quantity of magnesium hydroxide present. Each mL of 0.05 M edetate disodium is equivalent to 2.916 mg of $Mg(OH)_2$. ■2S (*USP27*)

(Official February 1, 2007)

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BRIEFING

Calcium Carbonate, Magnesia and Simethicone Tablets, *USP 26* page 303. It is proposed to change the title of this monograph to *Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40428-1

Calcium Carbonate, Magnesia, and Simethicone Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets**

BRIEFING

Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40428-1

Add the following:

■Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Calcium Carbonate, Magnesia, and Simethicone Tablets)

» Calcium Carbonate, Magnesia, and Simethicone Chewable Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of calcium carbonate ($CaCO_3$) and magnesium hydroxide [$Mg(OH)_2$], and an amount of polydimethylsiloxane [$–(CH_3)_2SiO–]_n$ that is not less than 85.0 percent and not more than 115.0 percent of the labeled amount of simethicone.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label it to indicate that the Chewable Tablets are to be chewed before swallowing. Label the Chewable Tablets to state the sodium content, in mg per Chewable Tablet, if it is greater than 5 mg per Chewable Tablet.

USP Reference standards ⟨11⟩—*USP Polydimethylsiloxane RS.*

Identification—

A: *Infrared Absorption* ⟨197S⟩—

Solution—Using Chewable Tablets, proceed to obtain IR absorption spectra as directed in the *Assay for polydimethylsiloxane* under *Alumina, Magnesia, and Simethicone Chewable Tablets.*

B: The addition of 1 N hydrochloric acid to a Chewable Tablet produces effervescence, and the resulting solution, after having been filtered, responds to the tests for *Calcium* ⟨191⟩.

C: Heat 2 Chewable Tablets in 20 mL of 1 N sulfuric acid. Cool, add 20 mL of alcohol, mix, and allow to stand for 30 minutes. Filter this solution, and to the filtrate add 2 mL of 1 N hydrochloric acid: this solution responds to the tests for *Magnesium* ⟨191⟩.

Uniformity of dosage units ⟨905⟩: meet the requirements for *Weight Variation* with respect to calcium carbonate and to magnesium hydroxide.

Acid-neutralizing capacity ⟨301⟩—Not less than 5 mEq of acid is consumed by the minimum single dose recommended in the labeling.

Defoaming activity—

Foaming solution—Dissolve 500 µg of FD&C Blue No. 1 and 1 g of octoxynol 9 in 100 mL of 0.1 N hydrochloric acid.

Procedure—[NOTE—For each test, use a clean, unused, 250-mL cylindrical glass jar.] Transfer a quantity of finely powdered Chewable Tablets, which has completely passed though an 80-mesh sieve, equivalent to 20 mg of simethi-

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cone, to a clean 250-mL cylindrical glass jar, fitted with a 50-mm cap, containing 100 mL of *Foaming solution* that has been warmed to 37°. Proceed as directed for *Procedure* in the test for *Defoaming activity* under *Simethicone,* beginning with "Cap the jar." The defoaming activity time does not exceed 45 seconds.

Sodium content (if so labeled)—

Lanthanum chloride solution—Prepare as directed in the *Assay for calcium carbonate and magnesium hydroxide.*

Dilute hydrochloric acid—Prepare as directed in the *Assay for polydimethylsiloxane.*

Standard solution—Transfer 2.542 g of sodium chloride, previously dried at 105° for 2 hours, to a 1000-mL volumetric flask, dissolve in water, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 4.0 mL of this solution to a second 100-mL volumetric flask containing 6.0 mL of *Dilute hydrochloric acid* and 2.0 mL of *Lanthanum chloride solution,* dilute with water to volume, and mix. This solution contains 2.0 µg of sodium (Na) per mL.

Test preparation—Transfer 3.0 mL of the aqueous layer retained from the preparation of the *Assay preparation* in the *Assay for polydimethylsiloxane* to a 50-mL volumetric flask containing 1.0 mL of *Lanthanum chloride solution,* dilute with water to volume, and mix.

Blank solution—Transfer 15.0 mL of *Dilute hydrochloric acid* and 5.0 mL of *Lanthanum chloride solution* to a 250-mL volumetric flask, dilute with water to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard solution* and the *Test preparation* at the sodium emission line at 589.0 nm with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a sodium hollow-cathode lamp and an air-acetylene flame, using the *Blank solution* as the blank. Calculate the mg of sodium (Na) in each Chewable Tablet taken by the formula:

$$(5C/6)(A/W)(A_U/A_S),$$

in which C is the concentration, in µg per mL, of sodium in the *Standard preparation, A* is the average weight, in mg, of each Chewable Tablet, W is the weight, in mg, of the portion of Chewable Tablets taken to prepare the *Assay preparation* in the *Assay for polydimethylsiloxane,* and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively. Each Chewable Tablet contains not more than the number of mg of sodium stated on the label.

Assay for polydimethylsiloxane—

Saccharin solution—Prepare a solution of saccharin in 4-methyl-2-pentanone containing 12.5 mg per mL.

Dilute hydrochloric acid—Mix 200 mL of hydrochloric acid with sufficient water to make 1000 mL.

Standard preparation—Dissolve a suitable quantity of USP Polydimethylsiloxane RS in 4-methyl-2-pentanone to obtain a stock solution having a known concentration of about 1 mg per mL. On the day of use, transfer 20.0 mL of this solution and 5.0 mL of *Saccharin solution* to a 250-mL volumetric flask, dilute with 4-methyl-2-pentanone to volume, and mix. This solution contains about 0.08 mg of USP Polydimethylsiloxane RS per mL.

Assay preparation—Weigh and finely powder not less than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of polydimethylsiloxane, to a 125-mL separator. Cautiously add 50.0 mL of *Dilute hydrochloric acid,* and swirl until the reaction subsides. Insert the stopper, and mix. Carefully release the pressure, add 50.0 mL of 4-methyl-2-pentanone, and mix for 10 minutes. Allow the layers to separate, and drain the aqueous layer into a suitable stoppered container. [NOTE—

Retain this aqueous layer for use in preparing the *Assay preparation* in the *Assay for calcium carbonate and magnesium hydroxide* and for the preparation of the *Test preparation* in the test for *Sodium content.*] Filter the organic layer through a filter containing 50 g of anhydrous sodium sulfate. Transfer 10.0 mL of the filtrate to a 50-mL volumetric flask, add 1.0 mL of *Saccharin solution,* dilute with methyl isobutyl ketone to volume, and mix.

Blank solution—Transfer 1.0 mL of *Saccharin solution* to a 50-mL volumetric flask, dilute with 4-methyl-2-pentanone to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* at the silicon emission line at 251.6 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a silicon hollow-cathode lamp and a nitrous oxide-acetylene flame, using the *Blank solution* as the blank. Calculate the quantity, in mg, of polydimethylsiloxane in each Tablet taken by the formula:

$$250C(A/W)(A_U/A_S),$$

in which C is the concentration, in mg per mL, of USP Polydimethylsiloxane RS in the *Standard preparation, A* is the average weight, in mg, of each Chewable Tablet, W is the weight, in mg, of the portion of Chewable Tablets taken to prepare the *Assay preparation,* and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.

Assay for calcium carbonate and magnesium hydroxide—

Lanthanum chloride solution—Transfer 26.8 g of lanthanum chloride to a 200-mL volumetric flask, add 100 mL of water, and carefully add 50 mL of hydrochloric acid. Mix, and allow to cool. Dilute with water to volume, and mix.

Dilute hydrochloric acid—Prepare as directed in the *Assay for polydimethylsiloxane.*

Calcium stock standard solution—Transfer 499.5 mg of primary standard calcium carbonate to a 200-mL volumetric flask, and add 10 mL of water. Carefully add 5 mL of *Dilute hydrochloric acid,* and swirl to dissolve the calcium carbonate. Dilute with water to volume, and mix. This solution contains 1000 µg of calcium (Ca) per mL.

Magnesium stock standard solution—Transfer 1.000 g of magnesium metal to a 1000-mL volumetric flask containing 10 mL of water, slowly add 10 mL of hydrochloric acid, and swirl to dissolve the metal. Dilute with water to volume, and mix. This solution contains 1000 µg of magnesium (Mg) per mL.

Calcium and magnesium standard preparation—To a 250-mL volumetric flask add 10.0 mL of *Calcium stock standard solution* and 5.0 mL of *Magnesium stock standard solution,* dilute with water to volume, and mix. This solution contains 40 µg of calcium (Ca) and 20 µg of magnesium (Mg) per mL. On the day of use, transfer 4.0 mL of this solution to a 100-mL volumetric flask containing 2.0 mL of *Lanthanum chloride solution,* dilute with water to volume, and mix. This solution contains 1.6 µg of calcium (Ca) and 0.8 µg of magnesium (Mg) per mL.

Assay preparation—Transfer an accurately measured volume of the aqueous layer retained from the preparation of the *Assay preparation* in the *Assay for polydimethylsiloxane,* equivalent to about 28 mg of calcium carbonate, to a 200-mL volumetric flask, dilute with water to volume, and mix. Transfer 3.0 mL of this solution to a 100-mL volumetric flask containing 2.0 mL of *Lanthanum chloride solution*, dilute with water to volume, and mix.

Blank solution—Transfer 5.0 mL of *Lanthanum chloride solution* to a 250-mL volumetric flask, dilute with water to volume, and mix.

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Procedure for calcium carbonate—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* at the calcium emission line at 422.7 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a calcium hollow-cathode lamp and an nitrous oxide-acetylene flame, using the *Blank solution* as the blank. Calculate the quantity, in mg, of calcium carbonate ($CaCO_3$) in each Tablet taken by the formula:

$$(100.09/40.08)(1000C/3V)(A/W)(A_U/A_S),$$

in which 100.09 is the molecular weight of calcium carbonate, 40.08 is the atomic weight of calcium, C is the concentration, in µg per mL, of calcium in the *Standard preparation, V* is the volume, in mL, of the aqueous layer retained from the preparation of the *Assay preparation* in the *Assay for polydimethylsiloxane* used to prepare the *Assay preparation, A* is the average weight, in mg, of each Chewable Tablet, W is the weight, in mg, of the portion of Chewable Tablets taken to prepare the *Assay preparation* in the *Assay for polydimethylsiloxane,* and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.

Procedure for magnesium hydroxide—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation* at the magnesium emission line at 285.2 nm, with a suitable atomic absorption spectrophotometer (see *Spectrophotometry and Light-Scattering* ⟨851⟩) equipped with a magnesium hollow-cathode lamp and a nitrous oxide-acetylene flame, using the *Blank solution* as the blank. Calculate the quantity, in mg, of magnesium hydroxide [$Mg(OH)_2$] in each Chewable Tablet taken by the formula:

$$(58.34/24.305)(1000C/3V)(A_U/A_S),$$

in which 58.34 is the molecular weight of magnesium hydroxide, 24.305 is the atomic weight of magnesium, C is the concentration, in µg per mL, of magnesium in the *Standard preparation, V* is the volume, in mL, of the aqueous layer retained from the preparation of the *Assay preparation* in the *Assay for polydimethylsiloxane* used to prepare the *Assay preparation, A* is the average weight, in mg, of each Chewable Tablet taken, W is the weight, in mg, of the portion of Tablets taken to prepare the *Assay preparation* in the *Assay for polydimethylsiloxane,* and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

(Official February 1, 2007)

BRIEFING

Carbamazepine Oral Suspension, *USP 26* page 324; **Doxepin Hydrochloride Oral Solution,** *USP 26* page 664; **Ergoloid Mesylates Oral Solution,** *USP 26* page 720; **Fluoxetine Oral Solution,** *USP 26* page 816; **Fluphenazine Hydrochloride Elixir,** *USP 26* page 822; **Haloperidol Oral Solution,** *USP 26* page 894; **Hydroxyzine Hydrochloride Oral Solution,** *USP 26* page 936; **Hydroxyzine Hydrochloride Syrup,** *USP 26* page 937; **Hydroxyzine Pamoate Oral Suspension,** *USP 26* page 939; **Meprobamate Oral Suspension,** *USP 26* page 1157; **Mesoridazine Besylate Oral Solution,** *USP 26* page 1167; **Nortriptyline Hydrochloride Oral Solution,** *USP 26* page 1339; **Perphenazine Oral Solution,** *USP 26* page 1438; **Perphenazine Syrup,** *USP 26* page 1439; **Phenytoin Oral Suspension,** *USP 26* page 1466; **Primidone Oral Suspension,** *USP 26* page 1539; **Thioridazine Oral Suspension,** *USP 26* page 1823; **Thiothixene Hydrochloride Oral Solution,** *USP 26* page 1829; **Trifluprom azine Oral Suspension,** *USP 26* page 1883. It is proposed to improve the standards in a number of oral solution, oral suspension, elixir, and syrup monographs by adding requirements for *Uniformity of dosage units* ⟨905⟩ for single-unit containers and requirements for *Deliverable volume* ⟨698⟩ for multiple-unit containers.

(PA3: S. Salado) RTS—40408-1

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Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S *(USP27)*

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S *(USP27)*

BRIEFING

Cefaclor Tablets. Because there is no existing monograph for this dosage form, a new monograph based on validated methods of analysis is being proposed. The monograph includes standards of quality for chewable Tablets. The liquid chromatographic procedures in the *Assay* are based on analyses performed with the 5-µm Hypersil ODS brand of L1 column. The typical retention time for cefaclor is about 9 minutes.

(PA7a: W. Wright; PSD: C. Okeke) RTS—39774-1

Add the following:

■Cefaclor Tablets

» Cefaclor Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of cefaclor ($C_{15}H_{14}ClN_3O_4S$).

Packaging and storage—Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Label chewable Tablets to include the word "chewable" in juxtaposition to the official name. The labeling indicates that chewable Tablets are to be chewed before being swallowed.

USP Reference standards ⟨11⟩—*USP Cefaclor RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—[To come]

Uniformity of dosage units ⟨905⟩: meet the requirements.

Water, *Method I* ⟨921⟩: not more than 5.0%.

Related compounds—

Solvent, Blank solution, Solution A, Solution B, Mobile phase, Standard solution, System suitability solution, and *Chromatographic system*—Proceed as directed for *Related compounds* under *Cefaclor.*

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the composite, equivalent to about 50 mg of cefaclor, to a 10-mL volumetric flask. Dissolve in *Solvent,* using brief sonication, if necessary, to achieve dissolution. Avoid heating. Dilute with *Solvent* to volume, mix, and filter. Use this *Test solution* within 3 hours if stored at room temperature, or within 20 hours when stored under refrigeration.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak area responses for all the peaks. Calculate the mg of each related compound in the portion of Tablets taken by the formula:

$$0.01CP(r_i / r_S),$$

in which the terms are as defined for *Related compounds* under *Cefaclor.* Not more than 1.0% of any individual cefaclor related compound is found; and the sum of all cefaclor related compounds found is not more than 3.0%, not including the contribution of any peak that gives a result of less than 0.1%.

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Assay—

Mobile phase, Standard preparation, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Cefaclor.*

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 75 mg of cefaclor, to a 250-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Sonicate, if necessary, to dissolve the cefaclor. Filter to obtain a clear solution.

Procedure—Proceed as directed in the *Assay* under *Cefaclor*. Calculate the quantity, in mg, of cefaclor ($C_{15}H_{14}ClN_3O_4S$) in the portion of Tablets taken by the formula:

$$5W_S(P/1000)(r_U/r_S),$$

in which the terms are as defined therein.■2S (*USP27*)

BRIEFING

Chlordiazepoxide Hydrochloride, *USP 26* page 417—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-10

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

USP Reference standards ⟨11⟩*—USP 2-Amino-5-chlorobenzophenone RS. USP Chlordiazepoxide Hydrochloride RS. USP Chlordiazepoxide Related Compound A RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

BRIEFING

Chloroquine, *USP 26* page 423—See briefing under *Acyclovir.*

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-2

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Chloroquine Phosphate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Chlorothiazide Oral Suspension, *USP 26* page 425; **Diazoxide Oral Suspension,** *USP 26* page 591; **Furosemide Oral Solution,** *USP 26* page 838; **Isosorbide Oral Solution,** *USP 26* page 1036; **Methyldopa Oral Suspension,** *USP 26* page 1200; **Sodium Citrate and Citric Acid Oral Solution,** *USP 26* page 1694. It is proposed to add sections for *Uniformity of dosage units* and *Deliverable volume* in order to specify requirements for Oral Solutions and Oral Suspensions packaged in single-unit containers and in multiple-unit containers, respectively.

(PA5: A. Wilk) RTS—40368-1

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Chlorpromazine Hydrochloride, *USP 26* page 434—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-11

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Chlorpromazine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Ciprofloxacin, *USP 26* page 457, page 2951 of the *First Supplement,* and page 1017 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Acyclovir.*

(PA7b: B. Davani) RTS—40237-3

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°. ~~; and avoid excessive heat.~~■2S (*USP27*)

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Add the following:

■**Labeling—**Where it is intended for use in preparing injectable dosage forms, the label states that it is sterile or must be subjected for further processing during the preparation of injectable dosage forms. Where it is intended for use in preparing Ciprofloxacin for Oral Suspension, it is so labeled. ■1S (*USP27*)

Add the following:

■**Microbial limits** ⟨61⟩—Where it is intended for use in preparing Ciprofloxacin for Oral Suspension, the total microbial count does not exceed 1000 cfu per g and the total combined molds and yeast count does not exceed 100 cfu per g. It also meets the requirement for absence of *Salmonella* and *Escherichia coli.*■1S (*USP27*)

Change to read:

Loss on drying ⟨731⟩—Dry it in vacuum at 120° for 6 hours: it loses not more than 1.0% of its weight,

■except that where it is labeled as intended for use in preparing Ciprofloxacin for Oral Suspension, it loses between 10% and 20% of its weight.■1S (*USP27*)

Change to read:

Residue on ignition ⟨281⟩: not more than 0.1%,

■except that where it is intended for use in preparing Ciprofloxacin for Oral Suspension, it is not more than 0.2%.■1S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that it is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩ and *Pyrogen* under *Ciprofloxacin Injection*. Where the label states that Ciprofloxacin must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Pyrogen* under *Ciprofloxacin Injection.*■1S (*USP27*)

BRIEFING

Ciprofloxacin Hydrochloride, *USP 26* page 458—See briefing under *Acyclovir.*

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-4

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Ciprofloxacin Hydrochloride is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Clarithromycin Extended-Release Tablets. Because there is no existing *USP* monograph for this article, a new monograph is being proposed. The liquid chromatographic procedure in the *Assay* is based on analyses performed with the 5-µm Nucleosil and the 5-µm Inertsil brands of L1 column. Typical retention times are about 4 and 6 minutes for clarithromycin and clarithromycin related compound A, respectively.

(PA7: W. Wright; PSD: C. Okeke) RTS—39803-1

Add the following:

■Clarithromycin Extended-Release Tablets

» Clarithromycin Extended-Release Tablets contain not less than 90.0 percent and not more than 115.0 percent of the labeled amount of clarithromycin ($C_{38}H_{69}NO_{13}$).

Packaging and storage—Preserve in well-closed containers, protected from light. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Clarithromycin RS. USP Clarithromycin Related Compound A RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the *Standard preparation,* as obtained in the *Assay.*

Drug release ⟨724⟩—[To come].

Loss on drying ⟨731⟩—Dry a portion of powdered Tablets in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 hours: it loses not more than 6.0% of its weight.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Mobile phase, Resolution solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Clarithromycin*.

Standard preparation—Prepare as directed for *Standard preparation* in the *Assay* under *Clarithromycin*, except to dilute an accurately measured volume of the stock solution quantitatively with *Mobile phase* to obtain a solution having a known concentration of about 400 µg of clarithromycin ($C_{38}H_{69}NO_{13}$) per mL.

Assay preparation—Finely powder an accurately counted number of Clarithromycin Extended-Release Tablets, equivalent to about 2000 mg of clarithromycin. With the aid of methanol quantitatively transfer the powder to a 500-mL volumetric flask, add about 350 mL of methanol, and shake by mechanical means for 30 minutes. Dilute with methanol to volume, mix, and allow any insoluble matter to settle. Transfer 3.0 mL of the supernatant to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Pass a portion of this solution through a filter having a porosity of 0.5 µm or finer, and use the filtrate as the *Assay preparation*.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Clarithromycin*. Calculate the quantity, in mg, of clarithromycin ($C_{38}H_{69}NO_{13}$) in each Extended-Release Tablet taken by the formula:

$$(50/3)(C/N)(r_U / r_S),$$

in which N is the number of Tablets taken, and the other terms are as defined therein.■2S (*USP27*)

BRIEFING

Cyanocobalamin Co 57 Oral Solution, *USP 26* page 502 and page 398 of *PF* 29(2) [Mar.–Apr. 2003]—See briefing under *Ferric Ammonium Citrate for Oral Solution*.

(RMI: A. Wilk) RTS—40369-2

Change to read:

» Cyanocobalamin Co 57 Oral Solution is a solution suitable for oral administration, containing Cyanocobalamin in which a portion of the molecules contain radioactive cobalt (^{57}Co) in the molecular structure. Cyanocobalamin Co 57 Oral Solution contains not less than 90.0 percent and not more than 110.0 percent of the labeled amount of ^{57}Co as cyanocobalamin expressed in megabecquerels (microcuries) per mL at the time indicated in the labeling. The cyanocobalamin content is not less than 90.0 percent and not more than

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110.0 percent of the labeled amount. ~~The specific activity is not less than 0.02 megabecquerel (0.5 microcurie) per µg of cyanocobalamin.~~

▲▲*USP27*
Cyanocobalamin Co 57 Oral Solution contains a suitable antimicrobial agent.

Add the following:

▲**Specific activity:** not less than 0.02 MBq (0.5 µCi) per µg of cyanocobalamin.▲*USP27*

Change to read:

Packaging and storage—Preserve in tight containers, protected from light,

▲and store in a cold place.▲*USP27*

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩ —

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Change to read:

Radiochemical purity— ~~[NOTE—Solutions of cyanocobalamin are light sensitive. Prepare the strips in diffuse light, and perform the development and drying steps in the absence of light.] Place 0.01 mL of a solution containing 1 mg of cyanocobalamin per mL about 45 mm from one end of a 25 mm × 300 mm strip of chromatographic paper (see *Chromatography* ⟨621⟩), and allow to dry. To the same area add a measured volume, such that it provides a count rate of not less than 20,000 counts per minute, of appropriately diluted Cyanocobalamin Co 57 Oral Solution, and allow to dry. Develop the chromatogram over a period of about 24 hours by descending chromatography, using a freshly prepared, homogeneous solution prepared by mixing 1 liter of secondary butyl alcohol, 1 mL of ammonium hydroxide, 20 mL of sodium cyanide solution (3.5 in 1000), and 300 mL of water (if phases separate, add 10 mL increments of secondary butyl alcohol, and shake until the mixture becomes homogeneous). Remove the paper strip from the apparatus when the cyanocobalamin spot has moved at least 75 mm from the point of application. Dry the chromatogram in air, and determine the radioactivity distribution by scanning with a suitable collimated radiation detector, or divide the strip horizontally into sections not exceeding 65 mm in width, and determine the radioactivity of the individual sections. The radioactivity of the cyanocobalamin band is not less than 95.0% of the total radioactivity.~~

▲*Mobile phase*—Prepare a solution of 10.0 g of dibasic sodium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 3.5. Prepare a mixture of this solution and methanol (73.5:26.5), mix, and degas. Use within 2 days.

Test solution—Use the Oral Solution.

Standard solution—Transfer about 10 mg of cyanocobalamin, accurately weighed, to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 2.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 361-nm detector, a gamma detector adjusted for ^{57}Co and a 4.6-mm × 25-cm stainless steel column that contains 5-µm packing L7. The flow rate is about 1 mL per minute.

Procedure—Inject about 100 µL of the *Standard solution* into the chromatograph, record the chromatogram for 30 minutes, and note the retention time of the cyanocobalamin peak. Inject 100 µL of the *Test solution* into the chromatograph, and record the chromatogram for three times the retention time of cyanocobalamin. Measure the peak areas using the gamma detector, and calculate the percentage of cyanocobalamin present as cyanocobalamin Co 57 using the formula:

$$100(r_U / r_T),$$

in which r_U is the cyanocobalamin Co 57 peak response obtained from the *Test solution,* and r_T is the total of all the peak area responses in the radiochromatogram obtained from the *Test solution.* Not less than 90% of the total radioactivity is found as cyanocobalamin Co 57.▲*USP27*

In-Process Revision

Add the following:

▲**Radionuclidic purity**—Using a suitable calibrated instrument (see *Radioactivity* ⟨821⟩) and standardized solutions of ^{58}Co, ^{57}Co, and ^{60}Co, record the gamma spectrum of the Oral Solution. The spectrum does not differ significantly from that of the standardized ^{57}Co solution. Determine the relative amounts of ^{58}Co, ^{57}Co, and ^{60}Co present. Cobalt 58 has a half-life of 70.9 days, and its presence is shown by 0.511- MeV and 0.811-MeV gamma photons. Cobalt 60 has a half-life of 5.27 years, and its presence is shown by 1.173-MeV and 1.333-MeV gamma photons. Not more than 1% of the total radioactivity is due to ^{60}Co; and not more than 2% of the total radioactivity is due to ^{58}Co, ^{60}Co, and other radionuclidic impurities.▲*USP27*

BRIEFING

Codeine Phosphate, *USP 26* page 506—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40343-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Codeine Phosphate RS.* ■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Cupric Chloride, *USP 26* page 522—See briefing under *Acyclovir.*

(PA7b: B.Davani; PSD: C. Okeke) RTS—40237-5

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

In-Process Revision

Add the following:

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

BRIEFING

Cyanocobalamin, *USP 26* page 525. It is proposed to revise the *Packaging and storage* section to include storage temperature conditions.

(DSN: L. Evans; PSD: C. Okeke) RTS—40373-1

Change to read:

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

■, and store at controlled room temperature.■2S (*USP27*)

BRIEFING

Cyanocobalamin Injection, *USP 26* page 526. It is proposed to revise the *Packaging and storage* section to include storage temperature conditions.

(DSN: L. Evans; PSD: C. Okeke) RTS—40372-1

Change to read:

Packaging and storage—Preserve in light-resistant, single-dose or multiple-dose containers, preferably of Type I glass

■, and store at controlled room temperature.■2S (*USP27*)

BRIEFING

Desoxycorticosterone Pivalate, *USP 26* page 557—See briefing under *Acepromazine Maleate*.

(VET: I. DeVeau; PSD: C. Okeke) RTS—40270-5

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate that it is for veterinary use only.

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

Change to read:

USP Reference standards ⟨11⟩—*USP Desoxycorticosterone Pivalate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Dextran 1, page 3089 of the *Second Supplement*. It is proposed to add a new section on *Other requirements* stating that where the label states that the article is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.

(BBP: L. Bhattacharyya) RTS—40300-1

Add the following:

■**Other requirements—**Where the label states that Dextran 1 is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Dextran 40, *USP 26* page 572 and page 399 of *PF* 29(2) [Mar.–Apr. 2003]. It is proposed to revise the *Packaging and storage* section to indicate appropriate storage temperatures. It is also proposed to add a new section on *Other requirements* stating that where the label states that the article is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.

(BBP:L. Bhattacharyya; PDS: C. Okeke) RTS—40300-2

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

USP Reference standards ⟨11⟩—*USP Dextran 40 RS.* ~~*USP Dextran Calibration RS.*~~

▲*USP Dextran 4 Calibration RS. USP Dextran 10 Calibration RS. USP Dextran 40 Calibration RS. USP Dextran 70 Calibration RS. USP Dextran 250 Calibration RS.*▲*USP27* *USP Dextran V_o Marker RS. USP Dextran 40 System Suitability RS. USP Endotoxin RS.*

Change to read:

Molecular weight distribution and weight and number average molecular weights—

Mobile phase—Prepare a suitable degassed and filtered solution containing 7.1 g of anhydrous sodium sulfate per liter in water.

Calibration solutions— ~~Separately dissolve each of the five USP Dextran Calibration RS in *Mobile phase* to obtain solutions containing 20 mg per mL.~~

▲Separately dissolve USP Dextran 4 Calibration RS, USP Dextran 10 Calibration RS, USP Dextran 40 Calibration RS, USP Dextran 70 Calibration RS, and USP Dextran 250 Calibration RS in *Mobile phase* to obtain solutions each containing 20 mg per mL.▲*USP27*

Marker solution—Prepare a solution in *Mobile phase* containing 3 mg of dextrose and 3 mg of USP Dextran V_o Marker RS per mL.

System suitability preparation—Prepare a solution of USP Dextran 40 System Suitability RS in *Mobile phase* containing 20 mg per mL.

Test preparation—Prepare a solution of Dextran 40 in *Mobile phase* containing 20 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a refractive index detector and three 7.5-mm × 30-cm columns containing packing L38, and maintained at a constant temperature. Chromatograph the *Marker solution,* and record the peak responses as directed for *Procedure:* the elution profile shows two peaks, the first due to the V_o marker, the second due to dextrose. Determine the void volume, V_o, of the system as the inflection point of the ascending part of the first peak. Determine the total volume, V_T, of the system as the maximum of the second peak; the tailing factor, *t,* of the dextrose peak is not more than 1.3; and the relative standard deviation of the ratio V_o/V_T is not more than 1%. ~~Chromatograph the *Calibration solutions,* and record the peak responses as directed for *Procedure.*~~

▲Chromatograph each of the *Calibration solutions* separately, and record the peak responses as directed for *Procedure.*▲*USP27*

Divide each profile into at least 60 vertical sections of equal volume increments. (The actual number of sections is represented by the variable a in the equations below). Record y_i, the height above the baseline, corresponding to each value of v_i, the volume eluted at that section. For each value of v_i, calculate the distribution coefficient, K_i, by the formula:

$$(v_i - V_o)/(V_T - V_o).$$

Find appropriate values of b_1, b_2, b_3, b_4, and b_5, using a suitable method,* that, when substituted in the equation:

$$M_i = b_5 + e^{(b_4 + b_1K_i + b_2K_i^2 + b_3K_i^3)},$$

and the resulting values of M_i substituted, along with their corresponding values of y_i, in the equation:

* The Gauss-Newton method, modified by Hartley [see D. Hartley *Technometrics,* **3** (1961)] and the G. Nilsson and K. Nilsson method [see G. Nilsson and K. Nilsson *J. Chromat,* **101,** 137 (1974)] is a suitable method. A curve-fitting program capable of nonlinear regression may be used.

$$\overline{M}_w = \sum_{i=1}^{a} (y_i M_i) \Big/ \sum_{i=1}^{a} y_i,$$

give values of weight average molecular weight, $\overline{M}_w$, within 5% of the labeled values for each of the *Calibration solutions* and 180 ± 2 for dextrose. Chromatograph the *System suitability preparation,* and record the peak responses as directed for *Procedure.* Calculate $\overline{M}_w$ of the total molecular weight distribution using the same method as directed for the *Calibration solutions,* but inserting the now known values of b_1, b_2, b_3, b_4, and b_5. It is between 39,000 and 46,000.

Similarly, calculate $\overline{M}_w$ of the high-fraction dextran eluted through section *n* by the formula:

$$\sum_{i=1}^{n} (y_i M_i) \Big/ \sum_{i=1}^{n} y_i,$$

in which *n* is defined by the relations:

$$\sum_{i=1}^{n} y_i \leq 0.1\left(\sum_{i=1}^{a} y_i\right), \text{ and}$$

$$\sum_{i=1}^{n+1} y_i > 0.1\left(\sum_{i=1}^{a} y_i\right).$$

It is between 111,000 and 135,000.

Similarly, calculate $\overline{M}_w$ of the low-fraction dextran eluted in and after section *m* by the formula:

$$\sum_{i=m}^{a} (y_i M_i) \Big/ \sum_{i=m}^{a} y_i,$$

in which *m* is defined by:

$$\sum_{i=m}^{a} y_i \leq 0.1\left(\sum_{i=1}^{a} y_i\right), \text{ and}$$

$$\sum_{i=m-1}^{a} y_i > 0.1\left(\sum_{i=1}^{a} y_i\right).$$

It is between 6,000 and 9,000.

Procedure—Chromatograph a 50-µL volume of the *Test preparation,* and record the peak responses. Calculate values of the weight average molecular weight, $\overline{M}_w$, of the total molecular weight distribution of the high-fraction dextran, and of the low-fraction dextran as directed for *System Suitability* under *Chromatography* ⟨621⟩ the values are between 35,000 and 45,000, not more than 120,000, and not less than 5,000, respectively. With the values of b_1, b_2, b_3, b_4, and b_5, obtained with the *Calibration solutions* under *Chromatographic system,* calculate the number average molecular weight, $\overline{M}_n$, of the total molecular weight distribution of the *Test preparation* by substituting the corresponding values of M_i, along with their corresponding values of y_i, in the equation:

$$\overline{M}_n = \sum_{i=1}^{a} y_i \Big/ \sum_{i=1}^{a} (y_i / M_i),$$

The number average molecular weight, $\overline{M}_n$, is between 16,000 and 30,000. Where Dextran 40 is labeled as intended for use in the preparation of injectables, the ratio $\overline{M}_w/\overline{M}_n$ is in the 1.4 to 1.9 range.

Add the following:

■**Other requirements**—Where the label states that Dextran 40 is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

In-Process Revision

BRIEFING

Dextran 70, *USP 26* page 575 and page 401 of *PF* 29(2) [Mar.–Apr. 2003]. It is proposed to revise the *Packaging and storage* section to indicate appropriate storage temperatures. It is also proposed to add a new section on *Other requirements* stating that where the label states that the article is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.

(BBP: L. Bhattacharyya; PSD: C. Okeke) RTS—40300-3

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

USP Reference standards ⟨11⟩*—USP Dextran 70 RS.* ~~*USP Dextran Calibration RS.*~~

▲*USP Dextran 4 Calibration RS. USP Dextran 10 Calibration RS. USP Dextran 40 Calibration RS. USP Dextran 70 Calibration RS. USP Dextran 250 Calibration RS.*▲*USP27 USP Dextran V_o Marker RS. USP Dextran 70 System Suitability RS. USP Endotoxin RS.*

Add the following:

■**Other requirements—**Where the label states that Dextran 70 is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Diatrizoate Meglumine, *USP 26* page 582—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-2

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩*—USP Diatrizoic Acid RS. USP Diatrizoic Acid Related Compound A RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Diatrizoate Sodium, *USP 26* page 585—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-3

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

In-Process Revision

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Diatrizoic Acid RS. USP Diatrizoic Acid Related Compound A RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

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

Change to read:

USP Reference standards ⟨11⟩—*USP Diatrizoic Acid RS. USP Diatrizoic Acid Related Compound A RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Diatrizoic Acid, *USP 26* page 586—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-4

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate whether it is anhydrous or hydrous.

BRIEFING

Diazepam, *USP 26* page 587—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-12

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

In-Process Revision

Change to read:

USP Reference standards ⟨11⟩—*USP Diazepam RS. USP Diazepam Related Compound A RS.*

■*USP Endotoxin RS.*■2S (*USP27*)
USP Nordazepam RS. USP 3-Amino-6-chloro-1-methyl-4-phenylcarbostyril RS.

Add the following:

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

BRIEFING

Diazoxide Oral Suspension, *USP 26* page 591—See briefing under *Chlorothiazide Oral Suspension.*

(PA5: A. Wilk) RTS—40368-2

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Dihydroergotamine Mesylate, *USP 26* page 434 and page 1463 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-11

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dihydroergotamine Mesylate RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Change to read:

Identification—
A: *Infrared Absorption* ⟨197K⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 50 µg per mL.
Medium: 70% alcohol. Absorptivities at 280 nm, calculated on the dried basis, do not differ by more than 3.0%.
C: ~~The principal spot from the *Test preparation* found in the test for *Related alkaloids* corresponds in R_f value to that obtained from the *Standard preparation.*~~

■The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*■2S (*USP27*)

Delete the following:

■~~**Related alkaloids—**~~
~~*Solvent mixture*—Mix 10 volumes of chloroform, 10 volumes of methanol, and 1 volume of ammonium hydroxide.~~
~~*Test preparation*—Prepare a solution of Dihydroergotamine Mesylate in *Solvent mixture* to contain 20 mg per mL.~~
~~*Standard preparation* and *Standard dilutions*—Prepare a solution of USP Dihydroergotamine Mesylate RS in *Solvent mixture* to contain 20 mg per mL *(Standard preparation).* Prepare a series of dilutions of *Standard preparation* in *Solvent mixture* to contain 0.40 mg, 0.20 mg, and 0.10 mg per mL *(Standard dilutions).*~~

In-Process Revision

~~*Procedure*—In a suitable chromatographic chamber arranged for thin-layer chromatography place a volume of a solvent system consisting of a mixture of chloroform and alcohol (9:1) sufficient to develop the chromatogram, cover, and allow to equilibrate for 30 minutes. Apply 5-µL portions of *Test preparation, Standard preparation,* and each of the three *Standard dilutions* to a suitable thin-layer chromatographic plate coated with a 0.25-mm layer of chromatographic silica gel. Allow the spots to dry, and develop the chromatogram until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with a solution prepared by dissolving 800 mg of *p*-dimethylaminobenzaldehyde in a cooled mixture of 80 g of alcohol and 20 g of sulfuric acid. The R_f value of the principal spot obtained from the *Test preparation* corresponds to that obtained from the *Standard preparation.* Estimate the concentration of any other spots observed in the lane for the *Test preparation* by comparison with the *Standard dilutions.* The spots from the 0.40-, 0.20-, and 0.10-mg-per-mL dilutions are equivalent to 2.0%, 1.0%, and 0.50% of impurities, respectively. The sum of the impurities is not greater than 2.0%.~~ ■2S (*USP27*)

Add the following:

■Chromatographic purity—

Diluent 1, Diluent 2, Solution A, Solution B, and *Mobile phase*—Proceed as directed in the *Assay.*

Standard solution 1— Use the *Standard preparation* prepared as directed in the *Assay.*

Standard solution 2—Dilute a known volume of *Standard solution 1* with *Diluent 2* and stepwise if necessary with *Diluent 2* to obtain a solution containing about 0.3 µg per mL.

Test solution—Use the *Assay preparation* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and a 4.0-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	60	40	equilibration
0–12	60–50	40–50	linear gradient
12–20	50–15	50–85	linear gradient
20–25	15	85	isocratic
24–25	15–60	85–40	linear gradient
25–31	60	40	re-equilibration

Chromatograph 10 µL of *Standard solution 1,* and record the peak areas as directed for *Procedure:* the tailing factor is between 0.8 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *Standard solution 2,* and record the peak areas as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

Procedure—Separately inject equal volumes (about 30 µL) of the *Standard solution 2* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the analyte peaks. Calculate the percentage of each impurity in the portion of Dihydroergotamine Mesylate taken by the formula:

$$5000\ (C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Dihydroergotamine Mesylate RS in the *Standard solution 2; W* is the weight, in mg, of Dihydroergotamine Mesylate taken to prepare the *Test solution;* r_i is the peak area of each impurity obtained from the *Test solution;* and r_S is the peak area of dihydroergotamine mesylate obtained from the *Standard solution 2:* not more than 0.5% of one individual impurity is found; not more than 1.0% of total impurities is found. ■2S (*USP27*)

Add the following:

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

In-Process Revision

Change to read:

Assay—

~~*Standard preparation*—Transfer about 10 mg of USP Dihydroergotamine Mesylate RS, accurately weighed, to a 200-mL volumetric flask, add 2 mL of methanol, dilute with tartaric acid solution (1 in 100) to volume, and mix.~~

~~*Assay preparation*—Using about 10 mg of Dihydroergotamine Mesylate, accurately weighed, prepare as directed for *Standard preparation.*~~

~~*Procedure*—Transfer 3.0 mL each of the *Standard preparation,* the *Assay preparation,* and tartaric acid solution (1 in 100) to provide the blank, to separate conical flasks. Add 6.0 mL of *p*-dimethylaminobenzaldehyde TS to each, shake, and allow to stand for 20 minutes. Concomitantly determine the absorbances of the solutions in 1-cm cells at the wavelength of maximum absorbance at about 585 nm, with a suitable spectrophotometer, against the blank. Calculate the quantity, in mg, of $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ in the portion of Dihydroergotamine Mesylate taken by the formula:~~

~~$$0.2C(A_U/A_S),$$~~

~~in which C is the concentration, in µg per mL, of USP Dihydroergotamine Mesylate RS in the *Standard preparation,* and A_U and A_S are the absorbances of the solutions from the *Assay preparation* and the *Standard preparation,* respectively.~~

■*Diluent 1*—Prepare a solution of 0.1 mL of phosphoric acid in 1000 mL of water.

Diluent 2—Prepare a mixture of *Diluent 1* and acetonitrile (60:40).

Solution A—Prepare a filtered and degassed mixture of water, 25 percent ammonia water, and 98% formic acid (1000:10:5). Adjust the pH to 8.50.

Solution B—Prepare a filtered and degassed mixture of acetonitrile and *Solution A* (80:20).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments to either solution as necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Dihydroergotamine Mesylate RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, with *Diluent 1* to obtain a solution having a known concentration of about 0.6 mg per mL. [NOTE—The final ratio of acetonitrile and *Diluent 1* should be similar to the final ratio obtained in the *Assay preparation.*]

Assay preparation—Transfer about 30 mg of Dihydroergotamine Mesylate, accurately weighed, to a 50-mL volumetric flask, dissolve with 20 mL of acetonitrile, dilute with *Diluent* 1 to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 280-nm detector and 4.0-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. The chromatograph is programmed as follows:

Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the tailing factor is between 0.8 and 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	60	40	equilibration
0–12	60–50	40–50	linear gradient
12–20	50–15	50–85	linear gradient
20–25	15	85	isocratic
24–25	15–60	85–40	linear gradient
25–31	60	40	re-equilibration

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the analyte peaks. Calculate the quantity, in mg, of $C_{33}H_{37}N_5O_5 \cdot CH_4O_3S$ in the portion of Dihydroergotamine Mesylate taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Dihydroergotamine Mesylate RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

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BRIEFING

Dihydrotachysterol Oral Solution, *USP 26* page 621; **Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution,** *USP 26* page 640; **Hyoscyamine Sulfate Oral Solution,** *USP 26* page 943; **Loperamide Hydrochloride Oral Solution,** page 3101 of the *Second Supplement* to *USP 26;* **Metoclopramide Oral Solution,** *USP 26* page 1218; **Prochlorperazine Oral Solution,** *USP 26* page 1550. It is proposed to improve the standards in monographs for a number of *Oral Solutions*. It is proposed to add requirements for *Uniformity of dosage units* ⟨905⟩ to apply to single-unit containers, and *Deliverable volume* ⟨698⟩ to apply to multiple-unit containers.

(PA4: E. Gonikberg) RTS—40419-1

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Dihydroxyaluminum Sodium Carbonate Tablets, *USP 26* page 624. It is proposed to change the title of this monograph to *Dihydroxyaluminum Sodium Carbonate Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40429-1

Dihydroxyaluminum Sodium Carbonate Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Dihydroxyaluminum Sodium Carbonate Chewable Tablets**

BRIEFING

Dihydroxyaluminum Sodium Carbonate Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40429-1

Add the following:

■Dihydroxyaluminum Sodium Carbonate Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Dihydroxyaluminum Sodium Carbonate Tablets)

» Dihydroxyaluminum Sodium Carbonate Chewable Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of CH_2AlNaO_5.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label the Chewable Tablets to indicate that they are to be chewed before swallowing.

Identification—A 1 in 10 suspension of powdered Chewable Tablets in 3 N hydrochloric acid responds to the tests for *Aluminum* ⟨191⟩ and for *Sodium* ⟨191⟩.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Acid-neutralizing capacity ⟨301⟩—Not less than 5 mEq of acid is consumed by the minimum single dose recommended in the labeling, and not less than the number of mEq calculated by the formula:

$$0.8(0.0278D),$$

in which 0.0278 is the theoretical acid-neutralizing capacity, in mEq, of CH_2AlNaO_5; and D is the quantity, in mg, of

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CH_2AlNaO_5 in the specimen tested, based on the labeled quantity.

Assay—

Edetate disodium titrant—Dissolve 18.6 g of edetate disodium in water to make 500 mL, and standardize as directed in the *Assay* under *Ammonium Alum*.

Procedure—Weigh and finely powder not fewer than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 300 mg of dihydroxyaluminum sodium carbonate, to a 250-mL beaker, and proceed as directed in the *Assay* under *Dihydroxyaluminum Sodium Carbonate,* beginning with "add 10 mL of 2 N sulfuric acid." Each mL of 0.1 *M Edetate disodium titrant* is equivalent to 14.40 mg of CH_2AlNaO_5.■2S (*USP27*)

(Official February 1, 2007)

BRIEFING

Diphenoxylate Hydrochloride and Atropine Sulfate Oral Solution, *USP 26* page 640—See briefing under *Dihydrotachysterol Oral Solution.*

(PA4: E. Gonikberg) RTS—40419-2

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Doxapram Hydrochloride, *USP 26* page 662—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-14

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Doxapram Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Doxepin Hydrochloride Oral Solution, *USP 26* page 664—See briefing under *Carbamazepine Oral Suspension*.

(PA3: S. Salado) RTS—40408-2

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Droperidol, *USP 26* page 674 and page 1473 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-15

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Droperidol RS.* ~~*USP 4,4′-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]-butyrophenone RS.*~~

■*USP Endotoxin RS.*■2S (*USP27*)

Change to read:

Limit of 4,4′-bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone—Dissolve about 30.0 mg of the sample in 70 mL of isopropyl alcohol in a 100-mL volumetric flask. Add 10.0 mL of 0.1 N hydrochloric acid, dilute with isopropyl alcohol to volume, and mix. ~~Concomitantly determine the absorbances of this solution and a Standard solution of USP 4,4′-Bis[1,2,3,6-tetrahydro-4-(2-oxo-1-benzimidazolinyl)-1-pyridyl]butyrophenone RS in the same medium at a concentration of 4.5 µg per mL,~~

■The absorptivity of the solution■2S (*USP27*) in 1-cm cells at the wavelength of maximum absorbance at about 330 nm, with a suitable spectrophotometer, using a 1 in 10 solution of 0.1 N hydrochloric acid in isopropyl alcohol as the blank ~~the absorbance of the test solution does not exceed that of the Standard solution, corresponding to not more than 1.5%.~~

■is not more than 0.7 (equivalent to limit of 1.5%).■2S (*USP27*)

Add the following:

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

BRIEFING

Emetine Hydrochloride, *USP 26* page 699—See briefing under *Acyclovir.*

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-6

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Cephaeline Hydrobromide RS. USP Emetine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

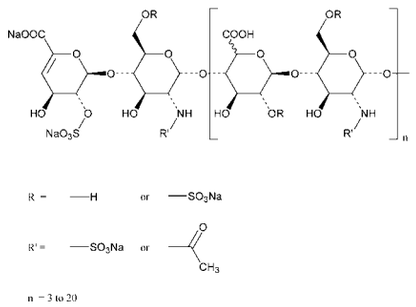
BRIEFING

Enoxaparin Sodium. Because there is no existing *USP* monograph for this article, a new monograph is being proposed.

(BBP: L. Bhattacharyya) RTS—39330-1; 40150-1

Add the following:

■Enoxaparin Sodium



[*9041-08-1*].

» Enoxaparin Sodium is the sodium salt of a depolymerized heparin. It is obtained by alkaline depolymerization of heparin benzyl ester. The starting material, heparin, is obtained exclusively from porcine intestinal mucosa. The majority of the components have a 4-enopyranose uronate structure at the nonreducing end of their chain. About 20 percent of the materials contain a 1,6-anhydro derivative on the reducing end of the chain, the range being between 15 and 25 percent. The weight-average molecular weight of Enoxaparin Sodium is 4,500 Da, the range being between 3,800 and 5,000 Da; about 16 percent has a molecular weight of less than 2,000 Da, the range being between 12.0 and 20.0 percent; about 74 percent has a molecular weight between 2,000

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and 8,000 Da, the range being between 68.0 and 82.0 percent. Not more than 18.0 percent has a molecular weight higher than 8,000 Da. The degree of sulfation is not less than 1.8 per disaccharide unit. It has a potency of not less than 90.0 and not more than 125.0 Anti-Factor X_a International Units per mg, and not less than 20.0 and not more than 35.0 Anti-Factor II_a International Units per mg, calculated on the dried basis. The ratio of anti-factor X_a activity to anti-factor II_a activity is between 3.3 to 5.3.

Packaging and storage—Preserve in tight containers, and store below 40°, preferably at room temperature.

USP Reference standards ⟨11⟩—*USP Benzyl Alcohol RS. USP Endotoxin RS. USP Enoxaparin Sodium RS. USP Enoxaparin Sodium Solution for Bioassays RS. USP Low-Molecular-Weight Heparin Molecular Weight RS.*

Identification—

A: *Ultraviolet Absorption* ⟨197U⟩—

Solution: 500 µg per mL.

Medium: 0.01 N hydrochloric acid. The spectra exhibit maxima at 231 ± 2 nm.

B: *^{13}C NMR spectrum* (see *Nuclear Magnetic Resonance* ⟨761⟩)—

Standard solution—Dissolve 200 mg of USP Enoxaparin Sodium RS in a mixture of 0.2 mL of deuterium oxide and 0.8 mL of water. Add 1 drop of deuterated methanol to serve as an internal reference.

Test solution—Dissolve 200 mg of Enoxaparin Sodium in a mixture of 0.2 mL of deuterium oxide and 0.8 mL of water. Add 1 drop of deuterated methanol.

Procedure—Transfer the *Standard solution* and the *Test solution* to NMR tubes of 5-mm diameter. Using a pulsed (Fourier transform) NMR spectrometer operating at not less than 75 MHz for ^{13}C, record the ^{13}C NMR spectra of the *Standard solution* and the *Test solution* at 40°. The spectra are similar.

C: The ratio of the numerical value of the anti-factor X_a activity, in Anti-Factor X_a International Units per mg, to the numerical value of the anti-factor II_a activity, in Anti-Factor II_a International Units per mg, as determined by the *Assay (anti-factor X_a activity)* and the *Anti-factor II_a activity,* respectively, is not less than 3.3 and not more than 5.3.

D: *Molecular weight distribution and weight-average molecular weight—*

Mobile phase—Prepare a 0.5 M lithium nitrate solution. Pass through a membrane filter having a porosity of 0.45 µm or less, and degas with helium.

Calibration solutions—Prepare two calibration solutions, *A* and *B*, by dissolving about 2 mg each of USP Low-Molecular-Weight Heparin Molecular Weight RS in 1 mL of the *Mobile phase*. Distribute the Reference Standards in alternating order of magnitude between solutions *A* and *B*.

Standard solution—Dissolve an accurately weighed quantity of about 10 mg of USP Enoxaparin Sodium RS in 1 mL of *Mobile phase*.

Test solution—Dissolve an accurately weighed quantity of about 10 mg of Enoxaparin Sodium in 1 mL of *Mobile phase*.

Chromatographic system (see *Chromatography* ⟨621⟩)—The high performance size exclusion chromatograph is equipped with a differential refractive index detector, a 6- × 40-mm guard column and two 7.8- × 300-mm analytical columns in series, both analytical and guard columns prepacked with L20 packing, and used at room temperature. The flow rate is about 0.6 mL per minute maintained constant to ±0.1%.

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Procedure—Separately inject 20 µL of *Calibration solutions A* and *B*, record the chromatograms, and measure the retention times. Inject in duplicate, 20 µL of each of the *Standard solution* and the *Test solution,* and record the chromatograms for a length of time to ensure complete elution, including salt and solvent peaks. Calculate the total area under each of the *Standard solution* and *Test solution* chromatograms, excluding salt and solvent peaks at the end.

Calibration curve—Plot the retention times on the y-axis against the peak molecular weights on the x-axis for the peaks in the chromatograms of *Calibration solutions A* and *B,* and fit the data to a third-order polynomial using a suitable gel permeation chromatography (GPC) software.

Calculations—Compute the data, using the same GPC software, to determine the weight-average molecular weight, M_W, for each of the duplicate chromatograms of the *Standard solution* and the *Test solution,* and take the average for each solution. Correct the mean value of M_W to the nearest 50. The *Chromatographic system* is suitable if M_W of USP Enoxaparin Sodium RS is within 150 Da of the labeled M_W value. The M_W for the *Test solution* is between 3,800 and 5,000 Da. Using the same software determine for each of the duplicate *Test solution* chromatograms the percentage of Enoxaparin Sodium chains with molecular weights lower than 2000 Da, M_{2000}, the percentage of Enoxaparin Sodium chains with molecular weights in the range 2000 and 8000 Da, $M_{2000–8000}$, and the percentage of Enoxaparin Sodium chains with molecular weights greater than 8000 Da, M_{8000}. Average the duplicate values and express to the nearest 0.5 %. M_{2000} is between 12.0% and 20.0%, $M_{2000–8000}$ is between 68.0% and 82.0%, and M_{8000} is not more than 18.0%.

E: It responds to the test for *Sodium* ⟨191⟩.

Appearance of solution (see *Clarity and Degree of Opalescence of Liquids* ⟨625⟩ and *Degree of Color of Liquids, Method I* ⟨627⟩)—

Test solution—Dissolve 1.0 g of Enoxaparin Sodium in 10 mL of water.

Procedure—The solution is clear and not more intensely colored than degree 6 of the range of *Reference Solutions* of the most appropriate color and not more opalescent than *Reference Suspension I.*

Specific absorbance (see *Spectrophotometry and Light-Scattering* ⟨851⟩)—

Test solution—Dissolve 50.0 mg of Enoxaparin Sodium in 100 mL of 0.01 N hydrochloric acid.

Procedure—Obtain the UV spectra of the *Standard solution* and the *Test solution* between 200 nm and 300 nm against 0.01 N hydrochloric acid blank. Calculate the specific absorbance at the wavelength of maximum absorbance at 231 ± 2 nm, with reference to the dried substance, using the following formula:

$$A \times 100 \times 1000 / [M \times 1 \times (100 - E)],$$

in which A is the absorbance at the wavelength of maximum absorbance; l is the pathlength (typically l = 1 cm); M is the weight, in mg, of Enoxaparin Sodium in the *Test solution;* and E is the loss on drying, in percent. The specific absorbance is between 14.0 and 20.0, calculated on the dried basis.

Bacterial endotoxins ⟨85⟩—It contains not more than 0.01 USP Endotoxin Unit per USP Unit of anti-factor X_a activity.

pH ⟨791⟩: between 6.2 and 7.7 in a 10.0% solution in water.

Loss on drying ⟨731⟩—Dry 1 g in a vacuum at 70° for 6 hours: it loses not more than 10.0% of its weight.

Nitrogen content, *Method II* ⟨461⟩: between 1.8% and 2.5%, calculated on the dried basis.

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Heavy metals, *Method I* ⟨231⟩—Prepare a 5% solution in water: the limit is not more than 0.0030%.

Sodium content (see *Spectrophotometry and Light-Scattering* ⟨851⟩)—

Cesium chloride solution—Prepare a solution of cesium chloride in 0.1 N hydrochloric acid containing 1.27 mg per mL.

Standard solutions—Dissolve an accurately weighed quantity of sodium chloride in *Cesium chloride solution* to obtain a solution having a known concentration of about 0.2% sodium. Dilute accurately measured volumes of this solution with *Cesium chloride solution* having known concentrations of 0.0025%, 0.0050%, and 0.0075% of sodium.

Test solution—Transfer an accurately weighed quantity of about 50.0 mg of Enoxaparin Sodium to a 100-mL volumetric flask, and dissolve in and dilute with *Cesium chloride solution* to volume.

Procedure—Concomitantly determine the absorbances of the *Cesium chloride solution* (blank), *Test solution*, and *Standard solutions* at 330.3 nm using a sodium hollow-cathode lamp and an air–acetylene flame. Using the absorbances of *Standard solutions,* determine the sodium content in the *Test solution* after appropriate blank correction. The sodium content, calculated on the dried basis, is between 11.3% and 13.5%.

Molar ratio of sulfate to carboxylate—

Mobile phase: carbon dioxide-free water.

Test solution—Dissolve an accurately weighed quantity of about 50 mg of Enoxaparin Sodium in 10 mL of carbon dioxide-free water.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph consists of two peristaltic pumps, a six-port injection valve, an ion detector, and two columns—one 1.5- × 2.5-cm column packed with an anion-exchange resin L## packing and one 1.5- × 7.5-cm column packed with a cation-exchange resin L## packing (see *Chromatography* ⟨621⟩). The outlet of the anion-exchange column is connected to the inlet of the cation-exchange column. The flow rate is about 1 mL per minute.

Procedure—[NOTE—Regenerate the anion-exchange column and the cation-exchange column with 1 N sodium hydroxide and 1 N hydrochloric acid, respectively, between two injections.] Inject the *Test solution* into the anion-exchange column, and collect the eluate from the cation-exchange column in a beaker at the outlet until the ion detector reading returns to the baseline value. Quantitatively transfer the eluate to a titration vessel containing a magnetic stirring bar, and dilute with carbon dioxide-free water to about 60 mL. Position the titration vessel on a magnetic stirrer and immerse the electrodes. Note the initial conductivity reading and titrate with approximately 0.1 N sodium hydroxide added in 100-µL portions. [NOTE—Prepare the sodium hydroxide solution in carbon dioxide-free water.] Record the burette reading and the conductivity meter reading after each addition of the sodium hydroxide solution.

Calculations—Plot the conductivity measurements on the y-axis against the volumes of sodium hydroxide added on the x-axis. The graph will have three linear sections—an initial downwards slope, a middle slight rise, and a final rise. For each of these sections draw the best-fit straight lines using linear regression analysis. At the points where the first and second straight lines intersect and where the second and third lines intersect, draw perpendiculars to the x-axis to determine the volumes of sodium hydroxide taken up by the sample at those points. The point where the first and second lines intersect corresponds to the volume of sodium hydroxide taken up by the sulfate groups (V_S). The point where the second and third lines intersect corresponds to the volume of

sodium hydroxide consumed by the sulfate and the carboxylate groups together (V_T). Calculate the molar ratio of sulfate to carboxylate by the formula:

$$V_S/(V_T - V_S).$$

The molar ratio of sulfate to carboxylate is not less than 1.8.

Benzyl alcohol content—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, methanol, and water (15:5:80 v/v).

Standard solution—Dissolve 100 mg of USP Benzyl Alcohol RS in 200 mL of water. Transfer 10 mL of this solution to a 100-mL volumetric flask, and dilute with water to volume. Transfer 5 mL of this solution to a 20-mL volumetric flask, and dilute with water to volume.

Test solution—Weigh 0.5 g of Enoxaparin Sodium into a 10-mL volumetric flask, and dissolve in 5.0 mL of 1 N sodium hydroxide. Allow to stand at room temperature for about 1 hour. Add 1.0 mL of glacial acetic acid, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 256-nm detector and a 4.6-mm × 15-cm stainless steel column that contains L7 packing. The flow rate is about 1.0 mL per minute maintained constant to ±10%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution,* record the chromatograms, and measure the peak responses.

Calculation—Calculate the percentage of benzyl alcohol in Enoxaparin Sodium taken by the formula,

$$(A_T \times C_S)/(A_S \times C_T),$$

in which C_T is the concentration, in mg per mL, of Enoxaparin Sodium; A_T is the benzyl alcohol peak area in the *Test solution;* C_S is the concentration, in mg per mL, of benzyl alcohol; and A_S is the area of the benzyl alcohol peak in the *Standard solution*. The percentage of benzyl alcohol is not more than 0.1%.

Anti-factor II_a activity—

Acetic acid solution, pH 7.4 Polyethylene glycol 6000 buffer, pH 7.4 buffer, pH 8.4 buffer, and *Antithrombin III solution*—Proceed as directed under *Assay (anti-factor X_a activity),* except that the concentration of the *Antithrombin III solution* is 0.5 Antithrombin III Unit per mL.

Thrombin human solution—Reconstitute thrombin human (see *Reagent Specifications* in the section *Reagents, Indicators and Solutions*) in water, and dilute in *pH 7.4 Polyethylene glycol 6000 buffer* to obtain a solution having a concentration of 5 Thrombin Units per mL.

Chromogenic substrate solution—Prepare a solution of a suitable chromogenic substrate for an amidolytic test (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) for thrombin in water to obtain a concentration of about 3 mM. Immediately before use, dilute with *pH 8.4 buffer* to 0.5 mM.

Standard solutions—Dilute USP Enoxaparin Sodium Solution for Bioassays RS with *pH 7.4 buffer* to obtain four dilutions having concentrations in the range between 0.015 and 0.075 USP Anti-Factor II_a Activity Unit per mL.

Test solutions—Proceed as directed under *Standard solutions* to obtain concentrations of Enoxaparin Sodium similar to those obtained for the *Standard solutions*.

Procedure—Proceed as directed under *Assay (anti-factor X_a activity),* except to use *Thrombin human solution* instead of *Factor X_a solution* and to use the *Antithrombin III solution* as described above.

Calculations—For each series, calculate the regression of the absorbance against log concentrations of the *Test solutions* and of the *Standard solutions,* and calculate the potency of the enoxaparin sodium in IU of anti-factor II_a

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activity per mg using statistical methods for parallel-line assays. The four independent relative potency estimates are then combined to obtain the final weighted mean, balanced by the adequate factor. Then calculate the confidence limits. Express the anti-factor II_a activity of Enoxaparin Sodium per mg, calculated on the dried basis.

Assay (anti-factor X_a activity)—

Acetic acid solution—Transfer 42 mL of glacial acetic acid to a 100-mL volumetric flask, dilute with water to volume, and mix.

pH 7.4 Polyethylene glycol 6000 buffer—Dissolve 6.08 g of tris(hydroxymethyl) aminomethane and 8.77 g of sodium chloride in 500 mL of water. Add 1.0 g of polyethylene glycol 6000, adjust with hydrochloric acid to a pH of 7.4., and dilute with water to 1000 mL.

pH 7.4 buffer—Dissolve 6.08 g of tris(hydroxymethyl)-aminomethane and 8.77 g of sodium chloride in 500 mL of water. Adjust with hydrochloric acid to a pH of 7.4, and dilute with water to 1000 mL.

pH 8.4 buffer—Dissolve 3.03 g of tris(hydroxymethyl)-aminomethane, 5.12 g of sodium chloride and 1.40 g of edetate sodium in 250 mL of water. Adjust with hydrochloric acid to a pH of 8.4, and dilute with water to 500 mL.

Antithrombin III solution—Reconstitute a vial of antithrombin III (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) in water to obtain a solution containing 5 Antithrombin III Units per mL. Dilute this solution with *pH 7.4 Polyethylene glycol 6000 buffer* to obtain a solution having a concentration of 1.0 Antithrombin III Unit per mL.

Factor X_a solution—Reconstitute an accurately weighed quantity of bovine factor X_a (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) in *pH 7.4 Polyethylene glycol 6000 buffer* to obtain a solution that gives an increase in absorbance value at 405 nm of not more than 0.20 absorbance units per minute when assayed as described below but using as an appropriate volume (*V,* in µL) of *pH 7.4 buffer* instead of *V* µL of the enoxaparin solution.

Chromogenic substrate solution—Prepare a solution of a suitable chromogenic substrate for amidolytic test (see *Reagent Specifications* in the section *Reagents, Indicators, and Solutions*) for factor X_a in water to obtain a concentration of about 3 mM. Dilute with *pH 8.4 buffer* to obtain a solution having a concentration of 0.5 mM.

Standard preparations—Dilute USP Enoxaparin Sodium Solution for Bioassays RS with *pH 7.4 buffer* to obtain four dilutions in the concentration range between 0.025 and 0.2 USP Anti-Factor X_a Units per mL.

Assay preparations—Proceed as directed for *Standard preparations* to obtain concentrations of Enoxaparin Sodium similar to those obtained for the *Standard preparations*.

Procedure—Label 18 suitable tubes: B1 and B2 for blanks; T1, T2, T3, and T4 each in duplicate for the dilutions of the *Assay preparations;* and S1, S2, S3, and S4 each in duplicate for the dilutions of the *Standard preparations*. [NOTE—Treat the tubes in the order B1, S1, S2, S3, S4, T1, T2, T3, T4, T1, T2, T3, T4, S1, S2, S3, S4, B2.] To each tube add the same volume, *V,* (20 to 50 µL) of *Antithrombin III solution* and an equal volume, *V,* of either the blank, *pH 7.4 buffer,* or an appropriate dilution of the *Assay preparations* or the *Standard preparations*. Mix, but do not allow bubbles to form. Incubate at 37° for 1.0 minute. Add to each tube volume 2*V* (40 to100 µL) of *Factor X_a solution,* and incubate for 1.0 minute. Add 5*V* (100 to 250 µL) volume of *Chromogenic substrate solution*. Stop the reaction after 4.0 minutes with 5*V* (100 to 250 µL) volume of *Acetic acid solution*. Measure the absorbance of each solution at 405 nm using a suitable spectrophotometer (see *Spectrophotometry*

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and Light-Scattering ⟨851⟩) against the blank B1. The reading of the blank B2 is not more than ±0.01 absorbance units.

Calculations—For each series, calculate the regression of the absorbance against log concentrations of the *Assay preparations* and of the *Standard preparations,* and calculate the potency of the enoxaparin sodium in IU of anti-factor II_a activity per mL using statistical methods for parallel-line assays. The four independent relative potency estimates are then combined to obtain the final weighted mean, balanced by the adequate factor. Its confidence limits are calculated. Express the anti-factor X_a activity of Enoxaparin Sodium per mg, calculated on the dried basis.■2S (*USP27*)

BRIEFING

Enoxaparin Sodium Injection. Because there is no existing *USP* monograph for this product, a new monograph is being proposed.

(BBP: L. Bhattacharyya) RTS—39330-2

Add the following:

■Enoxaparin Sodium Injection

» Enoxaparin Sodium Injection is a sterile solution of Enoxaparin Sodium in Water for Injection. Its potency value is not less than 90.0 percent and not more than 110.0 percent of the potency stated on the label in terms of USP Anti-factor X_a Units. It may contain, in multiple-dose containers, a suitable antimicrobial preservative, such as benzyl alcohol.

Packaging and storage—Preserve in single-dose or multiple-dose containers in Type I glass. Store between 20° and 25°, excursions permitted between 15° and 30°.

Labeling—Label it to indicate the amount (milligrams) of Enoxaparin Sodium in the total volume of contents. The label states also that the Enoxaparin Sodium starting material is porcine derived.

USP Reference standards ⟨11⟩—*USP Benzyl Alcohol RS. USP Endotoxin RS. USP Enoxaparin Sodium RS. USP Enoxaparin Sodium Solution for Bioassays RS.*

Identification—

A: Add 2 mL of water to the total content of a single-dose container or to 0.4 mL from a multiple-dose container and 1 mL of 2% w/v protamine sulfate solution in a glass test tube, and mix. A creamy white precipitate is formed.

B: *Ultraviolet Absorption* ⟨197U⟩—

Standard solution: 500 µg per mL.

Medium: 0.01 N hydrochloric acid. The spectra exhibit maxima at 231 ± 2 nm.

Test solution—Transfer the total content of a single-dose container or 0.4 mL from a multiple-dose container to a 100-mL volumetric flask. Dilute with *Medium* to volume.

C: It meets the requirements of the test for *Sodium* ⟨191⟩.

Clarity (see *Clarity and Degree of Opalescence of Liquids* ⟨625⟩)—The clarity of the solution does not exceed that of suspension I.

Color (see *Degree of Color of Liquids, Method I* ⟨627⟩)—The color of the solution is not more than degree 4 of the range of reference solution of the most appropriate color for a solution containing 100 mg of enoxaparin sodium per mL.

pH ⟨791⟩: between 5.5 and 7.5.

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Benzyl alcohol content *(if present)*—

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and water (1:1).

Standard solution—Transfer about 200 mg, accurately weighed, of USP Benzyl Alcohol RS to a 200-mL volumetric flask, and dilute with *Mobile phase* to volume.

Test solutions—Transfer 5.0 mL of the Injection to a 50-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 258-nm detector and a 4.0-mm × 25-cm stainless steel column that contains packing L1[1]. The flow rate is about 1.0 mL per minute maintained constant to ±10%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution,* record the chromatograms, and measure the peak responses. Calculate the percentage of benzyl alcohol in the portion of enoxaparin sodium solution taken by the formula:

$$(A_T \times M)/(A_S \times 20),$$

in which, A_T and A_S are areas of the benzyl alcohol peaks in the chromatograms of the *Test solution* and the *Standard solution,* respectively; and M is the mass of the benzyl alcohol dissolved to prepare the *Standard solution*. The percentage (w/v) of benzyl alcohol in the Injection is not less than 1.35% and not more than 1.65%.

Bacterial endotoxins ⟨85⟩—It contains less than 0.01 USP Endotoxin Units per unit of anti-factor X_a activity in USP Anti-factor X_a Units.

Free sulfate content—

Mobile phase—Prepare a 3.0 mM sodium carbonate solution. Make adjustments if necessary.

Standard sulfate stock solution—Prepare a solution of sodium sulfate in the *Mobile phase* in a suitable sulfate-free container such that the concentration of sulfate is accurately known at about 1 g per L. Transfer about 5 g, accurately weighed, of the solution to a similar container, and add *Mobile phase* to obtain about 25 g of solution.

Standard solutions—Prepare standard solutions at concentrations of 0.1, 0.5, 1, 2, 4, and 5 µg per g by appropriate dilution of the *Standard sulfate stock solution* in the *Mobile phase*.

System suitability solution—Prepare a solution containing 3 µg per mL of sulfate anion and 5 µg per mL of oxalate anion.

Test solutions—Transfer about 200 mg of a 100 mg per mL Enoxaparin Sodium Injection, accurately weighed, to a suitable previously tared sulfate-free vial. Add *Mobile phase* to obtain a total mass, M_S, of about 20 g.

Chromatographic system (see *Chromatography* ⟨621⟩)—The ion chromatograph is equipped with a conductivity detector and a 4-mm × 5-cm anion-exchange guard column, a 4-mm × 25-cm anion-exchange analytical column, prepacked with L## and L## packings (see *Chromatography* ⟨621⟩), respectively, and a micromembrane anion autosuppressor[2] or a suitable chemical suppression system. The flow rate is about 2.0 mL per minute.

Procedure—Chromatograph about 25 µL of the *System suitability solution*. The resolution between the sulfate and oxalate peaks is greater than 1. Separately inject 25 µL of the *Standard solutions* and the *Test solution* into the chromatograph and plot the standard curve of sulfate peak height as a function of sulfate concentration (in µg per g) in the *Standard solutions*. From the sulfate peak height in the chromatogram determine the concentration of sulfate, *T,* in µg

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[1] Available as Lichrospher 100 RP 18, Pore size 100 Å, Particle size 5 µm.

[2] Available as Anion Self-Regenerating Suppressor (ASRS) from Dionex Inc.

per g, in the *Test solution* using the standard curve. Calculate the percentage of free sulfate content (w/v) in the Injection taken using the formula:

$$T \times M_S / 10m,$$

in which m is the mass, in mg, of Enoxaparin Sodium Injection aliquoted to prepare the *Test solution*. The percentage of free sulfate is not more than 0.12%.

Anti-factor II_a activity—Proceed as directed for *Anti-factor II_a activity* under *Enoxaparin Sodium*.

Anti-factor X_a to anti-factor II_a ratio—The ratio of the numerical value of the anti-factor X_a activity in USP Anti-Factor X_a Units per mg to the numerical value of the anti-factor II_a activity in USP Anti-Factor II_a Units per mg, as determined by the *Assay (anti-factor X_a activity)* and the *Anti-factor II_a activity,* respectively, is not less than 3.3 and not more than 5.3.

Other requirements—It meets the requirements under *Injections* ⟨1⟩, *Particulate Matter in Injections* ⟨788⟩, and *Sterility Tests* ⟨71⟩.

Assay (anti-factor X_a activity)—Proceed as directed for *Assay (anti-factor X_a activity)* under *Enoxaparin Sodium*.■2S (*USP27*)

BRIEFING

Ergoloid Mesylates Oral Solution, *USP 26* page 720—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-3

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Ergotamine Tartrate, *USP 26* page 723—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-16

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Ergotamine Tartrate RS.

Add the following:

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

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BRIEFING

Etoposide Injection, *USP 26* page 772. It is proposed to revise the test for *Benzyl alcohol content* by deleting the reference to the internal standard because there is no internal standard used either in the *Standard preparation* or in the *Test preparation.*

(PA6: L. Evans) RTS—40362-1

Change to read:

Benzyl alcohol content *(if present)*—

Buffer solution, Mobile phase, System suitability solution, and *Chromatographic system*—Proceed as directed in the *Assay* under *Etoposide.*

Standard preparation—Transfer 0.75 mL of freshly distilled benzyl alcohol, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test preparation—Use the *Assay preparation.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the responses for the benzyl alcohol peaks. Calculate the quantity, in mg per mL, of benzyl alcohol in the volume of Injection taken by the formula:

$$500(C/V)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of benzyl alcohol in the *Standard preparation, V* is the volume of Injection taken, and r_U and r_S are the peak ~~response ratios of benzyl alcohol and the internal standard~~ ■responses of benzyl alcohol■2S (*USP27*) obtained from the *Test preparation* and the *Standard preparation,* respectively: between 90.0% and 110.0% of the labeled amount is found.

BRIEFING

Fentanyl Citrate, *USP 26* page 781—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40344-1

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Fentanyl Citrate RS.

Add the following:

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

BRIEFING

Ferumoxsil Oral Suspension, *USP 26* page 790—See briefing under *Ferric Ammonium Citrate for Oral Solution.*

(RMI: A. Wilk) RTS—40369-3

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS*:* meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS*:* meets the requirements.■2S (*USP27*)

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BRIEFING

Floxuridine, *USP 26* page 793—See briefing under *Acyclovir*. The *Bacterial endotoxins* test is not specified because the *Pyrogen* test is required in this monograph.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-7

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Flunixin Meglumine, *USP 26* page 799—See briefing under *Acepromazine Maleate*.

(VET: I. DeVeau; PSD: C. Okeke) RTS—40270-6

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Labeling—Label it to indicate that it is for veterinary use only.

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Flunixin Meglumine RS.

Add the following:

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

BRIEFING

Fluoxetine Oral Solution, *USP 26* page 816—See briefing under *Carbamazepine Oral Suspension*.

(PA3: S. Salado) RTS—40408-4

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Change to read:

Deliverable volume ⟨698⟩—

■FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: ■2S (*USP27*)
meets the requirements.

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BRIEFING

Fluphenazine Decanoate, *USP 26* page 820—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-17

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Fluphenazine Decanoate Dihydrochloride RS.

Add the following:

■**Other requirements—**Where the label states that Fluphenazine Decanoate is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩ and *Bacterial Endotoxins Test* ⟨85⟩, the limit being not more than 16.67 USP Endotoxin Units per mg of fluphenazine decanoate. Where the label states that Fluphenazine Decanoate must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* (not more than 16.67 USP Endotoxin Units per mg of fluphenazine decanoate).■2S (*USP27*)

BRIEFING

Fluphenazine Enanthate, *USP 26* page 821—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-18

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Fluphenazine Enanthate Dihydrochloride RS.

Add the following:

■**Other requirements—**Where the label states that Fluphenazine Enanthate is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩ and *Bacterial Endotoxins Test* ⟨85⟩, the limit being not more than 16.67 USP Endotoxin Units per mg of fluphenazine enanthate. Where the label states that Fluphenazine Enanthate must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* (not more than 16.67 USP Endotoxin Units per mg of fluphenazine enanthate).■2S (*USP27*)

BRIEFING

Fluphenazine Hydrochloride, *USP 26* page 821—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-19

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Fluphenazine Hydrochloride RS.

Add the following:

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

BRIEFING

Fluphenazine Hydrochloride Elixir, *USP 26* page 822—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-5

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ELIXIR PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ELIXIR PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Fosphenytoin Sodium, *USP 26* page 833 and page 1492 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-20

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Fosphenytoin Sodium RS. USP Phenytoin RS.*

■*USP Phenytoin Related Compound A RS.*■2S (*USP27*)
USP Phenytoin Related Compound B RS.

Change to read:

~~**Chromatographic purity—**~~

■**Related compounds**—■2S (*USP27*)
Buffer solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*
Standard solution—Dissolve accurately weighed quantities of ~~2,2-diphenylglycine,~~

■USP Phenytoin Related Compound A RS,■2S (*USP27*)
USP Phenytoin Related Compound B RS, and USP Phenytoin RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 3.0 µg per mL, 3.0 µg per mL, and 1.5 µg per mL, respectively.
Test solution—Transfer about 150 mg of Fosphenytoin Sodium, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.
Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for not less than six times the retention time of the major peak, and measure all of the peak responses. Calculate the percentage of phenytoin, phenytoin related compound B, and ~~2,2-diphenylglycine,~~

■phenytoin related compound A,■2S (*USP27*)
if present, in the portion of Fosphenytoin Sodium taken by the formula:

$$100(C_S / C_U)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of ~~USP Phenytoin RS~~

■the USP Reference Standard of the respective impurity■2S (*USP27*)
in the *Standard solution;* C_U is the concentration, in mg per mL, of Fosphenytoin Sodium in the *Test solution;* and r_i and r_S are the peak responses for each impurity obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of phenytoin is found; not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.

■[NOTE—Use the peak area and concentration of USP Phenytoin RS in the *Standard solution* as r_S and C_S, respectively, to calculate the percentage of the unknown impurities.]■2S (*USP27*)

Add the following:

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

BRIEFING

Furosemide Oral Solution, *USP 26* page 838—See briefing under *Chlorothiazide Oral Suspension.*

(PA5: A. Wilk) RTS—40368-3

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Gadodiamide, *USP 26* page 839—See briefing under *Adenosine.*

(RMI: A. Wilk) RTS—40329-5

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Gadodiamide is sterile, it meets the requirements for *Sterility* under *Gadodiamide Injection.*■2S (*USP27*)

BRIEFING

Gadoteridol, *USP 26* page 843—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-6

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Gadoteridol RS. USP Gadoteridol Related Compound A RS. USP Gadoteridol Related Compound B RS. USP Gadoteridol Related Compound C RS.

BRIEFING

Ganciclovir, page 2966 of the *First Supplement*. On the basis of comments received, the previously proposed revision to the *Packaging and storage* section, appearing on page 630 of *PF* 29(3) [May–June 2003], is being canceled and a new storage statement is proposed. See also the briefing under *Acyclovir*.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-8

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Ganciclovir RS. USP Ganciclovir Related Compound A RS.

Add the following:

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

BRIEFING

Gemfibrozil, *USP 26* page 849 and page 3100 of the *Second Supplement.* It is proposed to correct the calculations under the *Related compounds* test. In the absence of any adverse comment, it is proposed to implement this revision via the *First Interim Revision Announcement*, pertaining to *USP 27–NF 22,* with an official date of February 2, 2004.

(PA4:E. Gonikberg) RTS—40303-1

Change to read:

■**Related compounds—**■2S (*USP26*)
Mobile phase—Add 10 mL of glacial acetic acid to 750 mL of methanol in a 1000-mL volumetric flask, dilute with water to volume, mix, and pass through a membrane filter.

■*System suitability solution*—Dissolve accurately weighed quantities of USP Gemfibrozil RS, USP Gemfibrozil Related Compound A RS, and 2,5-dimethylphenol in *Mobile phase* to obtain a solution having known concentrations of about 0.2 mg per mL, 0.05 mg per mL, and 0.05 mg per mL, respectively.

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Standard solution—Transfer 10 mg each of USP Gemfibrozil RS and USP Gemfibrozil Related Compound A RS, both accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.■2S (*USP26*)

Test solution—Transfer about 100 mg of Gemfibrozil, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.
■■2S (*USP26*)

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 276-nm detector and a ■4.0-mm × 25-cm■2S (*USP26*) column that contains packing L1. The flow rate is about 1 mL per minute. ■Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.35 for 2,5-dimethylphenol, 1.0 for gemfibrozil, and 2.1 for gemfibrozil related compound A; and the relative standard deviation for replicate injection is not more than 3.0%.■2S (*USP26*)

Procedure—■Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for at least three times the retention time of gemfibrozil, and measure the areas for the major peaks. Calculate the percentage of gemfibrozil related compound A in the portion of Gemfibrozil taken by the formula:

~~$10C(r_U/r_S),$~~

$$\bullet 1000(C/W)(r_U/r_S),\bullet 1$$

in which C is the concentration, in mg per mL, of USP Gemfibrozil Related Compound A RS in the *Standard solution;*

•W is the weight, in mg, of Gemfibrozil taken to prepare the *Test solution;*•1
and r_U and r_S are the peak areas for gemfibrozil related compound A obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of gemfibrozil related compound A is found. Calculate the percentage of any other impurity in the portion of Gemfibrozil taken by the formula:

~~$100(r_i/r_u),$~~

$$\bullet 1000(C_G/W)(r_i/r_G),\bullet 1$$

in which

•C_G is the concentration, in mg per mL, of USP Gemfibrozil RS in the *Standard solution;*•1
r_i is the peak area of each individual impurity obtained from the *Test solution;* ~~and r_u is the sum of all of the peak areas obtained from the *Test solution.*~~

•r_G is the gemfibrozil peak area obtained from the *Standard solution;* and W is as defined above:•1
not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.■2S (*USP26*)

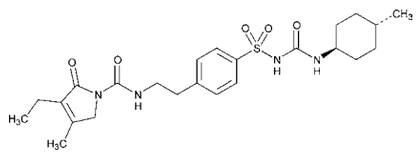
BRIEFING

Glimepiride. Because there is no existing *USP* monograph for this drug substance, a new monograph, based on validated methods of analysis, is being proposed. The liquid chromatographic procedure in the test for *Related compounds* and in the *Assay* is based on analyses performed with the Superspher 100 RP18 brand of L1 column. The typical retention time for glimepiride is about 17 minutes. The liquid chromatographic procedure in the test for *Limit of cis-isomer* is based on analyses performed with the Lichrosorb Diol brand of L20 column. The typical retention times for glimepiride and glimepiride *cis*-isomer are about 16 minutes and 14 minutes, respectively. The gas chromatographic procedure in the test for *Water* is based on analyses performed with the Optima 624 brand of G43 column. The approximate retention times for air, water, and dimethylformamide are about 1.6, 1.8, and 5.5 minutes, respectively.

(PA4: E. Gonikberg) RTS—40086-1

Add the following:

■Glimepiride



$C_{24}H_{34}N_4O_5S$ 490.62

1*H*-Pyrrole-1-carboxamide, 3-ethyl-2,5-dihydro-4-methyl-*N*-[2-[4-[[[[(4-methylcyclohexyl)amino]carbonyl]amino]sulfonyl]phenyl]ethyl]-2-oxo-, *trans*-.

1-[[4-[2-(3-Ethyl-4-methyl-2-oxo-3-pyrroline-1-carboxamido)ethyl]phenyl]sulfonyl]-3-(*trans*-4-methylcyclohexyl)urea [*93479-97-1*].

» Glimepiride contains not less than 97.0 and not more than 102.0 percent of $C_{24}H_{34}N_4O_5S$, calculated on the anhydrous basis.

Packaging and storage—Store in well-closed containers, at a temperature not exceeding 25°.

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USP Reference standards ⟨11⟩—*USP Glimepiride RS. USP Glimepiride Related Compound A RS. USP Glimepiride Related Compound B RS. USP Glimepiride Related Compound C RS. USP Glimepiride Related Compound D RS.*

Identification, *Infrared Absorption* ⟨197K⟩.

Water—

Diluent—Use dimethylformamide dried over a molecular sieve (2 mm; pore size: 0.4 nm).

Standard solution—Transfer about 100.0 mg of water, accurately weighed, into a 100-mL volumetric flask containing the *Diluent,* dilute with *Diluent* to volume, and mix.

Blank solution—Use the *Diluent.*

Test solution—Dissolve about 50 mg of Glimepiride, accurately weighed, in 1.0 ml of *Diluent.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a thermal conductivity detector, a 0.32-mm × 30-m fused silica column containing bonded phase G43 in a 1.8-µm film thickness, and a splitless injection system. The carrier gas is helium flowing at a rate of about 2.2 mL per minute. The temperature of the column is maintained at 80°, the injection port temperature is maintained at 200°, and the detector is maintained at 250°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the water peak and the air peak is not less than 2.0; and the relative standard deviation for replicate injections is not more than 10%. [NOTE—The approximate retention times for air, water, and dimethylformamide are about 1.6, 1.8, and 5.5 minutes, respectively.]

Procedure—Separately inject equal volumes (about 1 µL) of the *Blank solution,* the *Standard solution,* and the *Test solution* into the gas chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of water in the portion of Glimepiride taken by the formula:

$$(r_T - r_B)/(r_S - r_B)(W_S / W_U),$$

in which r_B, r_T, and r_S are the peak responses obtained from the *Blank solution,* the *Test solution,* and the *Standard solution,* respectively; W_S is the weight, in mg, of water taken to prepare the *Standard solution;* and W_U is the weight, in mg, of Glimepiride taken to prepare the *Test solution*. The water content is not more than 0.5%.

Residue on ignition ⟨281⟩**:** not more than 0.2%.

Heavy metals, *Method II* ⟨231⟩**:** 0.001%.

Limit of *cis*-isomer (glimepiride related compound A)—

Mobile phase—Transfer 100 mL of isopropyl alcohol into a 1-L volumetric flask, add 1 mL of glacial acetic acid, dilute with hexane to volume, filter, and degas.

System suitability stock solution—Dissolve about 1 mg of USP Glimepiride Related Compound A RS in 1 mL of methylene chloride. Add 3 mL of *Mobile phase,* and mix.

System suitability solution—Transfer about 10 mg of USP Glimepiride RS to a 20-mL volumetric flask, and dissolve in 5 mL of methylene chloride. Dilute with *Mobile phase* to volume, and mix. Transfer 5 mL of this solution to a separate flask, add 50 µL of the *System suitability stock solution,* and mix.

Test solution—Transfer about 10 mg of Glimepiride to a 20-mL volumetric flask, and dissolve in 5 mL of methylene chloride. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 228-nm detector and a 3-mm × 15-cm column containing 5-µm packing L20. The flow rate is about 0.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention

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times are 1.0 for glimepiride and not more than 0.9 for the glimepiride *cis*-isomer; and the signal-to-noise ratio of the glimepiride *cis*-isomer peak is not less than 15.

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, and measure the peak areas for the glimepiride cis-isomer and glimepiride. Calculate the percentage of glimepiride *cis*-isomer in the portion of Glimepiride taken by the formula:

$$100r_{cis} / (r_{cis} + r_G),$$

in which r_{cis} and r_G are the peak areas for the glimepiride *cis*-isomer and glimepiride, respectively: not more than 0.8% of the glimepiride *cis*-isomer is found.

Related compounds—

Mobile phase, Diluent, System suitability solution, and Chromatographic system—Prepare as directed in the *Assay.*

Test solution—Use the *Assay preparation.*

Diluted test solution 1—Dilute 5.0 mL of the *Test solution* with *Diluent* to 100.0 mL. Dilute 5.0 mL of the solution obtained with *Diluent* to 50.0 mL. This solution contains about 0.001 mg of glimepiride per mL.

Diluted test solution 2—Dilute 1.0 mL of *Diluted test solution 1* with *Diluent* to 10.0 mL.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and *Diluted test solutions 1* and *2* into the chromatograph, record the chromatograms, and measure the peak response for glimepiride obtained from *Diluted test solution 1* and the responses for all other peaks, other than the glimepiride peak, obtained from the *Test solution*. Disregard any peak with an area less than that of the glimepiride peak in the chromatogram obtained from *Diluted test solution 2.* Continue the elution for 2.5 times the retention time of the glimepiride peak. Calculate the percentage of each related compound (see *Table 1*) and any unknown impurity in the portion of Glimepiride taken by the formula:

$$100(C_S / C_T)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of glimepiride in *Diluted test solution 1;* C_T is the concentration, in mg per mL, of glimepiride in the *Test solution;* r_i is the peak response for each individual peak obtained from the *Test solution;* and r_S is the glimepiride peak obtained from *Diluted test solution 1.*

Table 1.

Relative Retention Time	Name	Limit (%)
0.2	Glimepiride related compound B[1]	0.4
0.3	Glimepiride related compound C[2]	0.1
1.1	Glimepiride related compound D[3]	0.2

[1] Glimepiride–sulfonamide
[2] Glimepiride–urethane
[3] Glimepiride-3-isomer

In addition to not exceeding the limits for each impurity in *Table 1*, not more than 0.1% of any other individual impurity is found; and not more than 0.5% of total impurities excluding glimepiride related compound B is found.

Assay—

Mobile phase—Dissolve 0.5 g of monobasic sodium phosphate in a mixture of 500 mL of water and 500 mL of acetonitrile. Adjust with phosphoric acid to a pH of 2.5 to 3.5.

Diluent—Prepare a mixture of acetonitrile and water (4:1).

Standard preparation —Dissolve an accurately weighed quantity of USP Glimepiride RS in *Diluent* to obtain a solution having a known concentration of about 0.2 mg per mL.

System suitability solution—Prepare a solution in *Diluent* containing 0.1 mg each of USP Glimepiride Related Compound B RS, USP Glimepiride Related Compound C RS, and USP Glimepiride Related Compound D RS per mL. Dilute 1 mL of this solution with the *Standard preparation* to 50 mL.

Assay preparation—Transfer about 20.0 mg of Glimepiride, accurately weighted, to a 100-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix. [NOTE—Keep the *Assay preparation* at a temperature not exceeding 12°, and store it no longer than 15 hours].

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 228-nm detector and a 4-mm × 25-cm column that contains packing L1. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and identify the glimepiride peak and the peaks due to the related compounds listed in *Table 1*. Record the peak responses as directed for *Procedure:* the resolution, *R,* between glimepiride related compound B and glimepiride related compound C is not less than 4.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of $C_{24}H_{34}N_4O_5S$ in the portion of Glimepiride taken by the formula:

$$10{,}000\ (C/W)[100/(100 - L)](r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Glimepiride RS in the *Standard preparation; W* is the weight, in mg, of Glimepiride taken to prepare the *Assay preparation; L* is the percentage of water as determined in the test for *Water;* and r_U and r_S are the peak responses for the glimepiride obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Glucagon, *USP 26* page 861—See briefing under *Acepromazine Maleate.*

(BNT: I. DeVeau) RTS—40270-7

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dextrose RS.*

■*USP Endotoxin RS.*■2S (*USP27*)
USP Glucagon RS.

Add the following:

■**Other requirements—**Where the label states that Glucagon is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Glucagon for Injection*. Where the label states that Glucagon must be subjected to further pro-

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cessing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Glucagon for Injection*.■2S (*USP27*)

BRIEFING

Gluconolactone, *USP 26* page 864. It is proposed to revise the test for *Lead* to correct an invalid reference.

(PA4: E. Gonikberg) RTS—40420-1

Change to read:

Lead ⟨251⟩—Prepare a *Test Preparation* as directed ~~for organic compounds,~~

■in the chapter,■2S (*USP27*)
and use 10 mL of *Diluted Standard Lead Solution* (10 µg of lead) for the test: the limit is 0.001%.

BRIEFING

Glycerin, *USP 26* page 867—See briefing under *Acyclovir*.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-9

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Glycerin is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Gold Sodium Thiomalate, *USP 26* page 871, page 3101 of the *Second Supplement,* and page 75 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Alfentanil Hydrochloride*.

(PA2: C. Anthony; PSD: C. Okeke) RTS—40345-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Gold Sodium Thiomalate is sterile, it meets the requirements for *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Gonadorelin Hydrochloride, *USP 26* page 872 and page 2552 of *PF* 27(3) [May–June 2001]. USP has had the opportunity to review the previously proposed revision, based on data submitted and published in *PF* 27(3), to increase the water content in this monograph. The data indicate that gonadorelin hydrochloride is stable when it is stored containing 7.0% water; therefore the proposal is being resubmitted by the USP Expert Committee on Biotechnology and Natural Therapeutics to allow for additional comments.

(BNT: I. DeVeau) RTS—39939-1

Change to read:

Water—[NOTE—Dry all glassware used in the following procedure at 105° for a minimum of 1 hour, and cool in a desiccator at room temperature. Store in a desiccator. Perform as many operations as possible in a low-humidity glove box.]

Anhydrous methanol—Wash about 150 g of 8- to 17-mesh type 3A molecular sieve with several 100-mL portions of methanol to remove the fine particles. Place the washed molecular sieve in a shallow glass dish, heat in an oven at 350° for 2 hours, and cool in a desiccator. Transfer the dry molecular sieve to a 1-liter glass container, add about 700 mL of methanol, insert a stopper, mix, and allow to stand in a desiccator for not less than 48 hours before using.

Standard solutions—Prepare solutions in *Anhydrous methanol* containing 0.4, 0.8, and 1.2 mg of distilled water per mL.

Test solution—[NOTE—Prepare immediately prior to use.] Transfer about 20 mg of Gonadorelin Hydrochloride, accurately weighed, to a vial, place a cap on the vial, add 800 µL of *Anhydrous methanol* by means of a 1000-µL gas-tight syringe, and swirl to mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a thermal conductivity detector and a 2-mm × 180-cm glass column packed with 80- to 100-mesh support S3. The column temperature is maintained at about 100°, and the injection port and detector temperatures are maintained at 130°. Helium is used as the carrier gas at a flow rate of about 30 mL per minute. Chromatograph the *Standard solution* containing 1.2 mg per mL, record the chromatograms, and measure the peak responses as directed for *Procedure:* the elution order is water, followed by a broad methanol peak; the retention time of the water peak is between 0.5 and 3 minutes; and the relative standard deviation for not less than three replicate injections is not more than 2.5%.

Procedure—Separately inject equal volumes (1 to 3 µL) of each of the *Standard solutions, Test solution,* and *Anhydrous methanol* into the chromatograph, and measure the responses for the first (water) and second (methanol) major peaks, correcting the peak areas obtained from the *Test solution* and the *Standard solutions* against the *Anhydrous methanol* blank. Plot the responses of the water peaks versus concentration, in mg per mL, of water in each of the *Standard solutions,* and determine the regression line using the least-squares method. The coefficient of variation from the regression line is not more than 3.0%. From the graph so obtained, determine the concentration, *C,* in mg per mL, of water in the *Test* solution. Calculate the percentage of water in the portion of Gonadorelin Hydrochloride taken by the formula:

$$80C/W,$$

in which *W* is the weight, in mg, of Gonadorelin Hydrochloride in the *Test solution:* not more than ~~3.0%~~

■7.0%■2S (*USP27*)
is found.

BRIEFING

Chorionic Gonadotropin, *USP 26* page 873 and page 1504 of *PF* 29(5) [Sept.–Oct. 2003]. It is proposed to add new sections on *Sterility* and *Labeling* providing that where the label states that it is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩. In addition, minor editorial style changes have been made.

(BNT: L. Bhattacharyya) RTS—40301-1

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩— ~~*USP Chorionic Gonadotropin RS.*~~

■*USP Human Chorionic Gonadotropin RS.*■2S (*USP27*)
USP Endotoxin RS.

Add the following:

■**Sterility** ⟨71⟩ (where it is labeled as sterile): meets the requirements.■2S (*USP27*)

Change to read:

Assay—

Standard preparations—Dissolve a suitable quantity of ~~USP Chorionic Gonadotropin RS~~

■USP Human Chorionic Gonadotropin RS.■2S (*USP27*)
in a diluent consisting of saline TS, freshly prepared to contain 1 mg per mL of bovine serum albumin and adjusted with sodium hydroxide TS to a pH between 6.9 and 8.0, to obtain a solution having a known concentration of 10 USP Chorionic Gonadotropin Units in each mL. Using the same diluent, prepare three *Standard preparations* such that the respective concentrations of chorionic gonadotropin constitute a geometric series such as 1:1.2:1.44 or 1:2:4 and such that the activity in each mL lies within the range of 0.1 to 1.0 Unit.

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Assay preparations—Following the procedure outlined for the *Standard preparations,* prepare solutions of Chorionic Gonadotropin to obtain three *Assay preparations* corresponding to those of the Standard.

The animals—Select 20- to 23-day-old female rats, but restrict the selection so that no rat is more than 30% heavier than the lightest. House the animals under uniform conditions of temperature, lighting, feeding, and watering. Mark the animals for identification, and divide them at random into groups of the same number but not less than 10 animals. Assign one group to each of the three *Standard preparations* and three *Assay preparations,* respectively.

Procedure—Inject each rat subcutaneously in the dorsal area with 0.20 mL of the solution to which it was assigned, at approximately the same time on each of three consecutive days. On the afternoon of the fifth day, sacrifice the animals, and excise the uterus from each animal by cutting through the cervix, stripping off the surrounding tissue, and severing at the utero-tubal junction. Gently press out the uterine fluid on moistened absorbent paper, and weigh the uterus to the nearest 0.2 mg, using a suitable balance.

Calculation—Tabulate the observed uterine weight for each rat, designated by the symbol *y,* for each dosage group of *f* rats. Proceed as directed in the *Assay* under *Corticotropin Injection,* beginning with "If the data from one or more rats." Compute the log confidence interval *L* (see *Confidence Intervals for Individual Assays* ⟨111⟩). If the confidence interval is more than 0.1938, which corresponds at $P = 0.95$ to confidence limits of 80% and 125% of the computed potency, repeat the assay until the combined data of two or more assays, redetermined as described under *Combination of Independent Assays* ⟨111⟩, meet this limit.

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Haloperidol RS. USP Haloperidol Related Compound A RS.

Change to read:

Melting range ⟨741⟩: between ~~147° and 152°,~~

■149° and 155°,■2S (*USP27*)
determined after drying in vacuum at 60° for 3 hours.

Add the following:

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

BRIEFING

Haloperidol, *USP 26* page 893 and page 1504 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-21

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

BRIEFING

Haloperidol Oral Solution, *USP 26* page 894—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-6

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Heparin Calcium, *USP 26* page 896. A new *Sterility* section is proposed providing that where the label states that Heparin Calcium is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.

(BBP: L. Bhattacharyya) RTS—40302-1

Add the following:

■**Sterility** ⟨71⟩ (where it is labeled as sterile)**:** meets the requirements.■2S (*USP27*)

BRIEFING

Heparin Sodium, *USP 26* page 897 and page 75 of *PF* 29(1) [Jan.–Feb. 2003]. A new *Sterility* section is proposed providing that where the label states that Heparin Sodium is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.

(BBP: L. Bhattacharyya) RTS—40302-2

Add the following:

■**Sterility** ⟨71⟩ (where it is labeled as sterile)**:** meets the requirements.■2S (*USP27*)

Change to read:

Anti-factor X_a activity—

~~*pH 8.4 buffer*—Dissolve amounts of tris(hydroxymethyl)aminomethane, edetic acid, and sodium chloride in water containing 0.1% of polyethylene glycol 6000 to obtain a solution having concentrations of 0.050 M, 0.0075 M, and 0.175 M, respectively. Adjust, if necessary, with hydrochloric acid or sodium hydroxide solution to a pH of 8.4.~~

~~*Blank solution*—Use *pH 8.4 buffer*.~~

~~*Antithrombin III solution*—Reconstitute an accurately weighed quantity of antithrombin III for amidolytic test (see *Reagents Specifications* in the section *Reagents, Indicators, and Solutions*) in *pH 8.4 buffer* to obtain a solution having a concentration of 1.0 Antithrombin III Unit per mL.~~

~~*Factor X_a solution*—Reconstitute an accurately weighed quantity of factor X_a for anti-factor X_a test (see *Reagents Specifications* in the section *Reagents, Indicators, and Solutions*) in water to obtain a solution containing about 20 Factor X_a Units per mL. Factor X_a Units are equivalent to nanokatalytic units (nkats). [NOTE—Whether employing Factor X_a Units or equivalent nkats, reconstitute as directed by the manufacturer of the reagent. Because of lot-to-lot differences due to variations among manufacturers in measuring anti-factor X_a activity, different quantities of factor X_a may be required. Different quantities of factor X_a may also be required because the absorbance value of factor X_a varies according to the chromogenic substrate used. This solution, when used in the reaction mixture containing the *Blank solution*, gives an absorbance rate change of 0.650 to 0.700 per minute, determined as directed for *Procedure*. Adjustments in potency are made, if necessary.]~~

~~*Chromogenic substrate solution*—Prepare a solution of chromogenic substrate for amidolytic test (see *Reagents Specifications* in the section *Reagents, Indicators, and Solutions*) in water to obtain a concentration of 2.5 mM or more.~~

~~*Standard solutions*—Dilute an accurately measured volume of USP Heparin Sodium RS with *pH 8.4 buffer*, and dilute accurately measured volumes of this solution with the same buffer to obtain a series of separate solutions having known concentrations of about 0.25, 0.188, 0.125, 0.0625, and 0.0312 USP Heparin Unit per mL.~~

~~*Test solutions*—Dissolve or dilute an accurately measured quantity of Heparin Sodium in *pH 8.4 buffer*, and dilute with *pH 8.4 buffer* to obtain separate solutions in a corresponding series of activities approximately equivalent to those of the *Standard solutions*.~~

~~*Procedure*—[NOTE—Each *Standard solution* and *Test solution* is made in duplicate. Two blank readings are made, one before the start of the test and another at the end. The two readings are similar to each other.] Add 600 µL of *pH 8.4 buffer*, 100 µL of *Antithrombin III solution*, and 100 µL of *Test solution* to a cuvette, mix, and incubate at 37° for 120 seconds. Add 100 µL of *Factor X_a solution*, mix immediately, and incubate at 37° for 120 seconds. Add 100 µL of *Chromogenic substrate solution*, mix immediately, and record the change in absorbance per minute at 405 nm and 37° in a spectrophotometer, or by reading the change in absorbance between 0 to 60 seconds. Repeat the procedure for each *Standard solution* and *Test solution*, and record the results.~~

~~*Calculations*—Convert to logarithms the absorbance values of the *Standard solutions*, and plot the log changes in absorbance on the *y* axis and the heparin concentrations on the *x* axis. Construct a straight line of best fit, using a least-squares linear regression analysis. Similarly treat the absorbance values of the *Test solutions*, and construct the *Test solutions* line. The regression lines for the *Test solutions* and the *Standard solutions* have a common intercept on the *y* axis at dose 0. Determine the slope for each regression line. Calculate the potency of Heparin Sodium taken by the formula:~~

~~$$P(s_u/s_s),$$~~

~~in which P is the potency of the *Standard solutions*, and s_u and s_s are the slopes of the lines from the *Test solutions* and the *Standard solutions*, respectively. Express the Anti-factor X_a potency of the *Test solution* as a percentage of the heparin concentration determined in the *Assay*. Calculate the percent anti-factor X_a activity against anticoagulant activity by the formula:~~

~~100(anti-factor X_a potency / anticoagulant potency).~~

~~Not less than 80% and not more than 120% is found.~~

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

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Antithrombin III solution—Reconstitute an accurately weighed quantity of antithrombin III (see *Reagent Specifications* under *Reagents, Indicators, and Solutions*) in *pH 8.4 buffer* to obtain a solution having a concentration of 1.0 Antithrombin III Unit per mL.

Factor X_a solution—Reconstitute an accurately weighed quantity of bovine factor X_a (see Factor X_a in *Reagent Specifications* under *Reagents, Indicators, and Solutions*) in *pH 8.4 Buffer* to obtain a solution that gives an absorbance value between 0.65 and 1.25 at 405 nm when assayed as described below but using 30 µL of *pH 8.4 Buffer* instead of the 30 µL of *Standard solutions* or *Test solutions.* [NOTE—*Factor X_a solution* contains about 3 nanokatalytic units per mL, but can vary depending upon the manufacturer of factor X_a or the substrate used.]

Chromogenic substrate solution—Prepare a solution of a suitable chromogenic substrate for amidolytic test (see *Reagent Specifications* under *Reagents, Indicators, and Solutions*) specific for factor X_a in water to obtain a concentration of about 1 mM.

Stopping solution—Prepare a 20% (v/v) solution of acetic acid in water.

Standard solutions—Dilute an accurately measured volume of USP Heparin Sodium RS with *pH 8.4 Buffer* to obtain at least 5 (out of 7 below) solutions having known activities of about 0.375, 0.3125, 0.25, 0.188, 0.125, 0.0625, and 0.0313 USP Heparin Unit per mL.

Test solutions—Dissolve or dilute an accurately measured quantity of Heparin Sodium in *pH 8.4 Buffer,* and dilute with the same buffer to obtain solutions having activities approximately equal to those of the *Standard solutions.*

Procedure—[NOTE—Perform the test with each *Standard solution* and *Test solution* in duplicate.] To each of a series of suitable plastic tubes placed in a water bath set at 37°, transfer 120 µL of *pH 8.4 Buffer.* Then separately transfer 30 µL of the different dilutions of *Standard solutions* or *Test solutions* to the tubes. Add 150 µL of *Antithrombin III solution,* prewarmed at 37° for 15 minutes, to each tube, mix, and incubate for 2 minutes. Add 300 µL of *Factor X_a solution,* prewarmed at 37° for 15 minutes, to each tube, mix, and incubate for 2 minutes. Add 300 µL of *Chromogenic substrate solution,* prewarmed at 37° for 15 minutes, to each tube, mix, and incubate for exactly 2 minutes. Add 150 µL of *Stopping solution* to each tube, and mix. Prepare a blank for zeroing the spectrophotometer by adding the reagents in reverse order, starting with the *Stopping solution* and ending with the addition of 150 µL of *pH 8.4 Buffer,* and excluding *Standard solutions* or *Test solutions.* Record the absorbance at 405 nm against the blank.

Calculations—Plot the log of the absorbance values of the *Standard solutions* and *Test solutions* versus heparin concentrations in USP Units. Construct separate straight lines of best fit using least-squares linear regression analyses for the *Standard solutions* and *Test solutions,* and determine the slope for each regression line. Calculate the potency of Heparin Sodium by the formula:

$$P(S_T / S_S),$$

in which P is the potency of USP Heparin Sodium RS; and S_T and S_S are the slopes of the lines from the *Test solutions* and *Standard solutions,* respectively. Express the Anti-factor X_a potency of the *Test solution* as a percentage of the heparin concentration determined in the *Assay.* Calculate the percent anti-factor X_a activity against anticoagulant activity by the formula:

100(anti-factor X_a potency / anticoagulant potency).

Not less than 80% and not more than 120% is found. ▲*USP27*

In-Process Revision

BRIEFING

Hydromorphone Hydrochloride, *USP 26* page 927—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40346-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Hydromorphone Hydrochloride RS.

Add the following:

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

BRIEFING

Hydroxyurea, *USP 26* page 934; **Hydroxyurea Capsules,** *USP 26* page 935. It has been reported that the current *Assay* procedure results in poor reproducibility and peak shape in the chromatogram of the *Resolution solution*. On the basis of these comments, it is proposed to replace the *Assay* with one that utilizes a buffer–methanol solution as the *Mobile phase*.

(PA6: L. Evans) RTS—40112-1; 40112-3

Change to read:

Assay—

~~*Mobile phase*—Use degassed water.~~

~~*Internal standard solution*—Dissolve uracil in water to obtain a solution having a concentration of about 0.12 mg per mL.~~

~~*Standard preparation*—Transfer about 50 mg of USP Hydroxyurea RS, accurately weighed, to a 50-mL volumetric flask, add 10 mL of *Internal standard solution,* dilute with water to volume, and mix.~~

~~*Resolution solution*—Dissolve suitable quantities of USP Hydroxyurea RS and hydroxylamine hydrochloride in water to obtain a solution containing about 1 mg and 4 mg per mL, respectively.~~

~~*Assay preparation*—Transfer about 50 mg of Hydroxyurea, accurately weighed, to a 50-mL volumetric flask, add 10 mL of *Internal standard solution,* dilute with water to volume, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 0.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed under *Procedure*: the resolution, *R*, between the hydroxylamine and hydroxyurea peaks is not less than 1.0. Chromatograph the *Standard preparation,* and record the peak responses as directed under *Procedure*: the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. The relative retention times are about 0.5 for hydroxyurea and 1.0 for uracil. Calculate the quantity, in mg, of $CH_4N_2O_2$ in the portion of Hydroxyurea taken by the formula:~~

$$50C(R_U/R_S),$$

~~in which *C* is the concentration, in mg per mL, of USP Hydroxyurea RS in the *Standard preparation,* and R_U and R_S are the response ratios of the hydroxyurea peak to the internal standard peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

■*Solution A*—Dissolve 1.7 g of tetrabutylammonium hydrogen sulfate and 1.74 g of dibasic potassium phosphate, anhydrous, in 1000 mL of water, and adjust with 1 N sodium hydroxide or 85% phosphoric acid to a pH of 5.0.

Solution B: methanol.

In-Process Revision

Mobile phase—Prepare a solution of filtered, degassed *Solution A* and *Solution B* (8.5:1.5). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Dissolve accurately weighed quantities of USP Hydroxyurea RS and hydroxylamine hydrochloride in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.4 mg per mL of each.

Standard preparation—Dissolve an accurately weighed quantity of USP Hydroxyurea RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.4 mg per mL.

Assay preparation—Transfer about 200 mg of Hydroxyurea, accurately weighed, to a 500-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 0.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the hydroxylamine and hydroxyurea peaks is not less than 1.5; for the hydroxyurea peak, the column efficiency is not less than 5000; and the tailing factor is not more than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $CH_4N_2O_2$ in the portion of Hydroxyurea taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Hydroxyurea RS in the *Standard preparation;* and r_U and r_S are the peak responses of the hydroxyurea peaks obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP27*)

BRIEFING

Hydroxyurea Capsules, *USP 26* page 935—See briefing under *Hydroxyurea*.

(PA6: L. Evans) RTS—40112-2

Change to read:

Assay—

~~*Mobile phase, Internal standard solution, Standard preparation, Resolution solution,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Hydroxyurea.*~~

~~*Assay preparation*—Remove, as completely as possible, the contents of not less than 20 Capsules, weigh, and place in a glass mortar. Grind to a fine powder, and transfer an accurately weighed portion of the powder, equivalent to about 2000 mg of hydroxyurea, to a 1000-mL volumetric flask. Add about 900 mL of water, sonicate for 5 minutes, stir with the aid of a magnetic stirrer for 30 minutes, dilute with water to volume, mix, and sonicate for an additional 5 minutes. Filter a portion of the resulting solution, discarding the first 10 mL of the filtrate. Transfer 25.0 mL of the clear filtrate to a 50-mL volumetric flask, add 10 mL of *Internal standard solution,* dilute with water to volume, and mix.~~

~~*Procedure*—Proceed as directed for *Procedure* in the *Assay* under *Hydroxyurea.* Calculate the quantity, in mg, of $CH_4N_2O_2$ in the portion of Capsules taken by the formula:~~

~~$2000C(R_U / R_S),$~~

~~in which C is the concentration, in mg per mL, of USP Hydroxyurea RS in the *Standard preparation,* and R_U and R_S are the response ratios of the hydroxyurea peak to the internal standard peak obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

In-Process Revision

■*Solution A, Solution B, Mobile phase, Resolution solution, Standard preparation,* and *Chromatographic system*—Prepare as directed in the *Assay* under *Hydroxyurea*.

Assay preparation—Remove, as completely as possible, the contents of not fewer than 20 Capsules. Grind to a fine powder, and transfer an accurately weighed portion of the powder, equivalent to about 200 mg of hydroxyurea, to a 500-mL volumetric flask. Add about 300 mL of *Mobile phase,* sonicate for 10 minutes, stir with the aid of a magnetic stirrer for 30 minutes, sonicate for an additional 10 minutes, and dilute as necessary with *Mobile phase* to volume. Filter a portion of the resulting solution, discarding the first 2 mL of the filtrate.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Hydroxyurea*. Calculate the quantity, in mg, of $CH_4N_2O_2$ in the portion of Capsules taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Hydroxyurea RS in the *Standard preparation;* and r_U and r_S are the peak responses for the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Hydroxyzine Hydrochloride, *USP 26* page 935—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-22

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Hydroxyzine Hydrochloride RS. USP p-Chlorobenzhydrylpiperazine RS.

Add the following:

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

BRIEFING

Hydroxyzine Hydrochloride Oral Solution, *USP 26* page 936—See briefing under *Carbamazepine Oral Suspension*.

(PA3: S. Salado) RTS—40408-7

Hydroxyzine Hydrochloride Oral Solution

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

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

In-Process Revision

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Hydroxyzine Hydrochloride Syrup, *USP 26* page 937—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-7

Hydroxyzine Hydrochloride Syrup

(Current title—not to change until June 1, 2005)
Monograph title change—to become official June 1, 2005
See **Hydroxyzine Hydrochloride Oral Solution**

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Hydroxyzine Hydrochloride Tablets, *USP 26* page 937. It is proposed to revise the *Dissolution* test to specify *Test 1* for the NDA product and *Test 2* for all approved generic products. A *Labeling* section is added accordingly.

(BPC: M. Marques) RTS—37276-1

Add the following:

■**Labeling**—When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.■2S (*USP27*)

Change to read:

Dissolution ⟨711⟩—

~~*Medium:* water; 800 mL.~~

~~*Apparatus*—Proceed as directed for *Uncoated Tablets* under *Disintegration* ⟨701⟩ beginning with "Place 1 Tablet in each of the six tubes of the basket", with these exceptions: (a) the disks are not used; (b) the apparatus is adjusted so that the bottom of the basket rack assembly descends to 1.0 ± 0.1 cm from the inside bottom surface of the vessel on the downward stroke; (c) the 10-mesh, stainless steel cloth in the basket rack is replaced with 40-mesh, stainless steel cloth; and (d) 40-mesh, stainless steel cloth is fitted to the top of the basket rack assembly if necessary to prevent any dosage unit from floating out of the tubes of the assembly.~~

~~*Time:* 45 minutes.~~

~~*Procedure*—Determine the amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 230 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Hydroxyzine Hydrochloride RS in the same *Medium.* Calculate the amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ dissolved in each Tablet.~~

~~*Tolerances*—Not less than 75% of the labeled amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ is dissolved in 45 minutes.~~

■TEST 1—

Medium: water, 250 mL.

Apparatus 3 (see *Drug Release* ⟨724⟩): 30 dips per minute.

Time: 45 minutes.

Procedure—Determine the amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 230 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of

In-Process Revision

USP Hydroxyzine Hydrochloride RS in the same *Medium.* Calculate the amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ dissolved per Tablet.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ is dissolved in 45 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: water, 900 mL.

Apparatus 2: 50 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 230 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Hydroxyzine Hydrochloride RS in the same *Medium.* Calculate the amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ dissolved per Tablet.

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_{21}H_{27}ClN_2O_2 \cdot 2HCl$ is dissolved in 45 minutes.■2S (*USP27*)

BRIEFING

Hydroxyzine Pamoate Oral Suspension, *USP 26* page 939—See briefing under *Carbamazepine Oral Suspension*.

(PA3: S. Salado) RTS—40408-8

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Hyoscyamine Sulfate Oral Solution, *USP 26* page 943—See briefing under *Dihydrotachysterol Oral Solution*.

(PA4: E. Gonikberg) RTS—40419-3

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698 ⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Imipramine Hydrochloride, *USP 26* page 956—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-23

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Desipramine Hydrochloride RS.*

■*USP Endotoxin RS.*■2S (*USP27*)
USP Iminodibenzyl RS. USP Imipramine Hydrochloride RS.

Add the following:

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

BRIEFING

Indigotindisulfonate Sodium, *USP 26* page 961—See briefing under *Acepromazine Maleate*.

(GTB: I. DeVeau; PSD: C. Okeke) RTS—40270-8

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Indigotindisulfonate Sodium RS.

Add the following:

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

BRIEFING

Indocyanine Green, *USP 26* page 966 and page 765 of *PF* 28(3) [May–June 2002]—See briefing under *Acepromazine Maleate*.

(GTB: I. DeVeau; PSD: C. Okeke) RTS—40270-9

Change to read:

» Indocyanine Green contains not less than ~~94.0 percent and not more than 105.0 percent~~

■89.0 percent and not more than 100.0 percent■2S (*USP27*) of $C_{43}H_{47}N_2NaO_6S_2$, calculated on the dried basis. It contains not more than 5.0 percent of sodium iodide, calculated on the dried basis.

Change to read:

Packaging and storage—Preserve in well-closed containers.

In-Process Revision

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Assay—Dissolve a quantity of Indocyanine Green, equivalent to about 100 mg of dried indocyanine green and accurately weighed, in methanol, and dilute quantitatively and stepwise with methanol to obtain a solution containing about 2 µg per mL. Dissolve a quantity of USP Indocyanine Green RS, accurately weighed

■and corrected for labeled purity,■2S (*USP27*)
in methanol, and dilute quantitatively and stepwise with methanol to obtain a Standard solution having a known concentration of about 2 µg per mL. Concomitantly determine the absorbances of both solutions in 1-cm cells at the wavelength of maximum absorbance at about 785 nm, with a suitable spectrophotometer, using methanol as the blank. Calculate the quantity, in mg, of $C_{43}H_{47}N_2NaO_6S_2$ in the Indocyanine Green taken by the formula:

$$50C(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Indocyanine Green RS in the Standard solution; and A_U and A_S are the absorbances of the solution of Indocyanine Green and the Standard solution, respectively.

BRIEFING

Insulin, *USP 26* page 973 and page 2969 of the *First Supplement*—See briefing under *Acepromazine Maleate*.

(BNT: I. DeVeau) RTS—40270-10

Change to read:

Labeling—Label it to indicate the one or more animal species to which it is related, as pork, as beef, or as a mixture of pork and beef. If the Insulin is purified, label it as such.

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

Add the following:

■**Other requirements—**Where the label states that Insulin is sterile, it meets the requirements for *Sterility* under *Insulin Injection*.■2S (*USP27*)

BRIEFING

Insulin Human, *USP 26* page 976—See briefing under *Acepromazine Maleate*.

(BNT: I. DeVeau) RTS—40270-11

Change to read:

Labeling—Label it to indicate that it has been prepared by microbial synthesis or that it is derived by enzymatic modification of insulin from pork pancreas.

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

Change to read:

Other requirements—It meets the requirements for *Zinc content* under *Insulin.*

■Where the label states that Insulin Human is sterile, it meets the requirements for *Sterility* under *Insulin Human Injection.*■2S (*USP27*)

BRIEFING

Inulin, *USP 26* page 980 and page 1508 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-7

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

In-Process Revision

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Dextrose RS.*

■*USP Endotoxin RS.*■2S (*USP27*)
USP Fructose RS.

Change to read:

pH, Chloride, ~~Sulfate,~~

■■2S (*USP27*)
Iron, and Reducing sugars—Dissolve 10.0 g in 20 mL of boiling water in a 100-mL volumetric flask, allow to cool, dilute with water to volume, and mix. Use the solution for the following tests.

pH ⟨791⟩—The pH of the solution is between 4.5 and 7.0.

Chloride ⟨221⟩—A 10-mL portion of the solution shows no more chloride than corresponds to 0.20 mL of 0.020 N hydrochloric acid (0.014%).

~~*Sulfate*—To 10 mL of the solution add 1 mL of barium chloride TS: no turbidity is produced.~~

■■2S (*USP27*)

Iron—To 10 mL of the solution add 0.5 mL of hydrochloric acid and 3 drops of potassium ferrocyanide TS: the solution does not become blue within 1 minute.

Reducing sugars—To 2 mL of the solution add 5 mL of alkaline cupric tartrate TS: no reduction occurs at room temperature, and only slight reduction occurs after one minute of boiling.

Add the following:

■**Sulfate** ⟨221⟩—A 1.0 g portion shows no more sulfate than corresponds to 0.5 mL of 0.020 N sulfuric acid (0.05%). [NOTE—Inulin should be dissolved in 30 to 40 mL of water with gentle warming, prior to dilution to final volume.]■2S (*USP27*)

Add the following:

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

BRIEFING

Iodipamide, *USP 26* page 990—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-8

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP 3-Amino-2,4,6-triiodobenzoic Acid RS.*

■*USP Endotoxin RS.*■2S (*USP27*)
USP Iodipamide RS.

Change to read:

Other requirements—It meets the requirements of the tests for *Iodine and iodide* and *Heavy metals* under *Diatrizoic Acid*.

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

BRIEFING

Iodixanol, *USP 26* page 991 and page 79 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Adenosine.*

(RMI: A. Wilk) RTS—40329-9

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS*■2S (*USP27*)
USP Iodixanol RS. ~~*USP Iodixanol Related Compound A RS.*~~

▲*USP Iohexol Related Compound B RS.*▲*USP27*
USP Iodixanol Related Compound C RS. USP Iodixanol Related Compound D RS. USP Iodixanol Related Compound E RS.

Change to read:

Limit of free aromatic amine—

N-(1-Naphthyl)ethylenediamine dihydrochloride solution—Prepare a fresh solution of *N*-(1-naphthyl)ethylenediamine dihydrochloride (3 in 1000) in a mixture of propylene glycol and water (70:30).

Blank solution—Add 15 mL of water to a 25-mL volumetric flask.

Standard stock solution—Dissolve an accurately weighed quantity of ~~USP Iodixanol Related Compound A RS,~~

▲USP Iohexol Related Compound B RS,▲*USP27*
and quantitatively dilute with water to obtain a solution having a known concentration of about 10 µg per mL.

Standard solution—Transfer 10.0 mL of the *Standard stock solution* and 5 mL of water to a 25-mL volumetric flask.

Test solution—Transfer about 200 mg of Iodixanol, accurately weighed, to a 25-mL volumetric flask, add 15 mL of water, and mix.

Procedure—Treat the *Standard solution,* the *Test solution,* and the *Blank solution* as follows. Place the flask in an ice bath for 5 minutes. Add 1.5 mL of 6 N hydrochloric acid, mix by swirling, add 1.0 mL of sodium nitrite solution (2 in 100), mix, and allow to stand in the ice bath for 4 minutes. Remove the flask from the ice bath, add 1.0 mL of 4% sulfamic acid solution, and swirl gently until gas evolution ceases. Add 1.0 mL of *N-(1-Naphthyl)ethylenediamine dihydrochloride solution,* mix, dilute with water to volume, mix, and allow to stand for 5 minutes. Transfer the solution obtained from the *Test solution* and the solution obtained from the Standard solution to separate color-comparison tubes. The solution obtained from the *Test solution* is lighter than the solution obtained from the *Standard solution:* not more than 0.05% is found. If the solution obtained from the *Test solution* is about the same color or darker than the solution obtained from the *Standard solution,* proceed as follows. Concomitantly determine the absorbances of the solution obtained from the *Test solution,* the solution obtained from the *Standard solution,* and the solution obtained from the *Blank solution* in 5-cm cells, at the wavelength of maximum absorbance at about 495 nm, using the solution obtained from the *Blank solution* to zero the spectrophotometer. Calculate the percentage of free aromatic amine in the portion of Iodixanol taken by the formula:

$$(C/W)[(A_U - A_B)/(A_S - A_B)],$$

in which C is the concentration, in µg per mL, of ~~USP Iodixanol Related Compound A RS~~

▲USP Iohexol Related Compound B RS▲*USP27*
in the *Standard solution; W* is the weight, in mg, of Iodixanol taken to prepare the *Test solution;* and A_U, A_B, and A_S are the absorbances of the final solutions obtained from the *Test solution, Blank solution,* and *Standard solution,* respectively: not more than 0.05% is found.

Add the following:

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

BRIEFING

Iohexol, *USP 26* page 996 and page 1508 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-10

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

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Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Iohexol RS. USP Iohexol Related Compound A RS. USP Iohexol Related Compound B RS. USP Iohexol Related Compound C RS.

Change to read:

Related compounds—

Solution A: acetonitrile.

Solution B: water.

Mobile phase—Use variable mixtures of a degassed mixture of *Solution A* and *Solution B* as directed for *Chromatographic system.*

System suitability solution—Dissolve accurately weighed quantities of USP Iohexol RS, USP Iohexol Related Compound A RS, and USP Iohexol Related Compound C RS in water to obtain a solution having known concentrations of about 1.5 mg per mL, 0.0075 mg per mL, and 0.0069 mg per mL, respectively.

Test solution—Transfer 75.0 mg of Iohexol, accurately weighed, to a 50-mL volumetric flask, dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm stainless steel column that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed to provide variable mixtures of *Solution A* and *Solution B:* the percentage of *Solution A* increases from 1% to 13% at a rate of 0.2% per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the retention time for the *O*-alkylated compounds is between 1.1 and 1.4 relative to 1.0 for the *exo*-isomer of iohexol; the resolution, *R,* between iohexol related compound A and iohexol related compound C is not less than 20.0; and the peak area of iohexol related compound C is 0.5% ± 0.1% by comparison to the total area of all of the peaks in the chromatogram.

Procedure—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of *O*-alkylated compounds

■and any other individual impurity peak, excluding peaks with a retention time between 0.84 (relative to the *endo*-isomer of iohexol [first main peak]) and the *endo*-isomer of iohexol,■2S (*USP27*)
in the portion of Iohexol taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the response of each impurity; and r_s is the sum of the responses of all of the peaks: not more than 0.1% of any individual impurity is found; not more than 0.6% of *O*-alkylated compounds is found; and the sum of all impurities,

■other than *O*-alkylated compounds,■2S (*USP27*)
is not more than 0.3%.

Add the following:

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

BRIEFING

Iopamidol, *USP 26* page 998—See briefing under *Adenosine.*

(RMI: A. Wilk) RTS—40329-11

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Iopamidol RS. USP Iopamidol Related Compound A RS. USP Iopamidol Related Compound B RS.

Add the following:

■**Other requirements—**Where the label states that Iopamidol is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Iopamidol Injection.* Where the

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label states that Iopamidol must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Iopamidol Injection.*■2S (*USP27*)

BRIEFING

Iophendylate, *USP 26* page 1000—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-12

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Iothalamic Acid, *USP 26* page 1005—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-13

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP 5-Amino-2,4,6-triiodo-N-methylisophthalamic Acid RS.*

■*USP Endotoxin RS.*■2S (*USP27*)
USP Iothalamic Acid RS.

Add the following:

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

BRIEFING

Ioversol, *USP 26* page 1006—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-14

Change to read:
Packaging and storage—Preserve in well-closed containers.
■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:
USP Reference standards ⟨11⟩—
■*USP Endotoxin RS.*■2S (*USP27*)
USP Ioversol RS. USP Ioversol Related Compound A RS. USP Ioversol Related Compound B RS.

Add the following:

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

BRIEFING

Ioxaglic Acid, *USP 26* page 1008—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-15

Change to read:
Packaging and storage—Preserve in well-closed containers.
■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Ioxaglic Acid is sterile, it meets the requirements for *Sterility* under *Ioxaglate Meglumine and Ioxaglate Sodium Injection*.■2S (*USP27*)

BRIEFING

Ioxilan, *USP 26* page 1008—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-16

Change to read:
Packaging and storage—Preserve in well-closed, light-resistant containers.
■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Ioxilan is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Isoflurane, *USP 26* page 1021. In the test for *Related compounds,* to clarify preparation of the *Internal standard solution* and the *Standard solution* used in the standard addition analysis, it is proposed to add a note specifying that the Isoflurane used to prepare these solutions is the same Isoflurane that is under test. It is also proposed to revise the *Packaging and storage* requirement to include a recommended storage temperature, in accordance with the current policy of the USP Expert Committee on Packaging, Storage, and Distribution (PSD). In addition, minor editorial style changes have been made.

(PA1: K. Russo; PSD: C. Okeke) RTS—40164-1

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

Related compounds—

■[NOTE—The *Internal standard solution* and the *Standard solution* are prepared using the same Isoflurane that is under test.]■2S (*USP27*)

Internal standard solution—Transfer about 1 g of normal butyl acetate, accurately weighed, to a 100-mL volumetric flask, dilute with Isoflurane to volume, and mix.

Standard solution—To 95 mL of Isoflurane in a 100-mL volumetric flask, add 10.0 µL of ▲USP Isoflurane Related Compound A RS,▲*USP26* 7.0 µL of ▲USP Isoflurane Related Compound B RS,▲*USP26* 10.0 µL of acetone, and 250 µL of *Internal standard solution,* dilute with Isoflurane to volume, and mix. It contains 0.01% of ▲isoflurane related compound A,▲*USP26* 0.007% of ▲isoflurane related compound B,▲*USP26* and 0.01% of acetone.

Test solution—To 20.0 mL of Isoflurane add 50.0 µL of *Internal standard solution,* and mix. It contains about 0.0025% (w/v) of normal butyl acetate.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2.4-mm × 3.7-m nickel or stainless steel column packed with 10% phase G31 and 15% phase G18 on 60- to 80-mesh sodium hydroxide-washed support S1C. The carrier gas is helium, flowing at a rate of about 25 mL per minute. The chromatograph is programmed as follows. Initially the temperature of the column is maintained at 65° for 7 minutes, and then the temperature is increased at a rate of 4° per minute to 110°. The injection port temperature is maintained at about 150°, and the detector is maintained at about 200°. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the tailing factor for the normal butyl acetate peak is not more than 1.5; and the relative standard deviation for replicate injections of the ratio of the response of the acetone peak to the response of the normal butyl acetate peak is not more than 2.0%.

Procedure—Separately inject equal volumes (about 3 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms for 40 minutes, and measure the responses for all the peaks. Separately calculate the percentages of acetone, ▲isoflurane related compound A,▲*USP26* and ▲isoflurane related compound B▲*USP26* in the portion of Isoflurane taken by the formula:

$$P[R_U/(R_S - R_U)],$$

in which P is the percentage of the relevant analyte in the *Standard solution;* and R_U and R_S are the peak response ratios obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.01% of acetone, not more than 0.01% of ▲isoflurane related compound A,▲*USP26* and not more than 0.007% of ▲isoflurane related compound B▲*USP26* are found. Calculate the percentage of any other individual impurity by the formula:

$$P[R_i/(R_S - R_i)],$$

in which P is the percentage of ▲isoflurane related compound B▲*USP26* in the *Standard solution;* R_i is the peak response ratio of any individual impurity to the internal standard obtained from the *Test solution;* and R_S is the peak response ratio of ▲isoflurane related compound B▲*USP26* to the internal standard obtained from the *Standard solution:* not more than 0.003% of any other individual impurity is found.

BRIEFING

Isoniazid, *USP 26* page 1025—See briefing under *Acyclovir.*

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-11

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Isoniazid RS.

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Add the following:

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

BRIEFING

Isosorbide Oral Solution, *USP 26* page 1036—See briefing under *Chlorothiazide Oral Suspension*.

(PA5: A. Wilk) RTS—40368-4

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Ketamine Hydrochloride, *USP 26* page 1045 and page 1039 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Acepromazine Maleate*.

(VET: I. DeVeau; PSD: C. Okeke) RTS—40270-12

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Ketamine Hydrochloride RS. USP Ketamine Related Compound A RS.

Change to read:

Related compounds—

~~*Buffer, Mobile phase,* and *System suitability solution*—Proceed as directed in the *Assay*.~~

~~*Standard solution*—Transfer 4.0 mL of the *System suitability solution* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix to obtain a solution having known concentrations of about 0.002 mg each of USP Ketamine Hydrochloride RS and USP Ketamine Related Compound A RS per mL.~~

~~*Test solution*—Transfer about 100 mg of Ketamine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, add about 30 mL of *Mobile phase,* and sonicate to dissolve. Dilute with *Mobile phase* to volume, and mix.~~

~~*Chromatographic system*—Proceed as directed in the *Assay*. To evaluate the system suitability requirements, use the *System suitability solution* and the *Standard preparation,* as prepared in the *Assay*.~~

~~*Procedure*—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of ketamine related compound A in the portion of Ketamine Hydrochloride taken by the formula:~~

$$5000(C/W)(r_U/r_S),$$

~~in which *C* is the concentration, in mg per mL, of USP Ketamine Related Compound A RS in the *Standard solution; W* is the weight, in mg, of Ketamine Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak responses for ketamine related compound A obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of ketamine related compound A is found. In the chromatogram of the *Test solution,* the response of no other, unknown, impurity is greater than 0.3% of the ketamine peak response; and the sum of the responses of all unknown impurity peaks is not greater than 1.0% of the ketamine peak response.~~

■*Mobile phase*—Dissolve 0.95 g of sodium 1-hexanesulfonate in 1 liter of a solution consisting of a mixture of water and acetonitrile (3:1). Add 4 mL of acetic acid, and mix.

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~~*Ketamine hydrochloride standard stock solution*—Dissolve an accurately weighed quantity of USP Ketamine Hydrochloride RS in *Mobile phase,* sonicating if necessary, to obtain a solution having a concentration of 1 mg per mL.~~

~~*Resolution solution*—Dissolve an accurately weighed quantity of USP Ketamine Related Compound A RS in *Mobile phase,* sonicating if necessary, to obtain a solution having a concentration of 0.5 mg per mL. To 1 mL of this solution, add 0.5 mL of *Ketamine hydrochloride standard stock solution,* and dilute with *Mobile phase* to 100 mL. [NOTE—Prepare immediately before use.]~~

Standard solution—Dissolve accurately weighed quantities of USP Ketamine Hydrochloride RS and USP Ketamine Related Compound A RS in *Mobile phase* (sonicate if necessary) to prepare a solution containing about 0.005 mg per mL of each compound. Prepare immediately before use.

Test solution—Transfer an accurately weighed quantity of about 50.0 mg of Ketamine Hydrochloride to a 50-mL volumetric flask. Dissolve in and dilute with *Mobile phase* to volume, sonicating if necessary. ~~Dilute 1.0 mL of the solution so obtained to 10.0 mL with *Mobile phase.* Dilute 1.0 mL of the resulting solution to 20.0 mL with *Mobile phase.*~~

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 215-nm detector and a 4.0-mm × 4.0-mm guard column with a 4.0-mm × 12.5-cm analytical column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the ~~*Resolution solution,*~~ *Standard solution,* and record the peak responses as directed for *Procedure:* the order of elution is ketamine hydrochloride followed by ketamine related compound A; the retention time of ketamine hydrochloride is between 3.0 and 4.5 minutes (if necessary, adjust the concentration of water and acetonitrile); the resolution, *R,* between ketamine hydrochloride and ketamine related compound A is not less than 2.0; and the tailing factor is not greater than 1.5.

Procedure—Separately inject equal volumes (about 20 µL) of the ~~*Resolution solution,*~~ *Standard solution,* and the *Test solution* into the chromatograph, record the chromatograms, identify the ketamine hydrochloride and ketamine related compound A peaks, and measure the areas of the major peaks. Calculate the area percentage of each impurity, relative to ketamine hydrochloride, taken by the formula:

~~$100(r_i/r_u)$,~~

~~in which r_i and r_u are the peak areas of the impurity and ketamine hydrochloride, respectively, in the *Test solution.*~~

$$5000(C/W)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Ketamine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Ketamine Hydrochloride taken to prepare the *Test solution;* r_i is the peak area of each individual impurity peak in the *Test solution;* and r_S is the response of the ketamine hydrochloride peak obtained from the *Standard solution.* Not more than 0.1% of ketamine related compound A is found; the response of no other unknown impurity is greater than 0.3% of the ketamine peak area; and the sum of the responses of all unknown impurity peaks is not greater than 1.0% of the ketamine peak response. ■1S (*USP27*)

Add the following:

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

In-Process Revision

Change to read:

Assay—

Buffer—Dissolve 5.75 g of monobasic ammonium phosphate in 1000 mL of water. Add 6 mL of triethylamine, and adjust with phosphoric acid to a pH of 3.0.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer* and methanol (65:35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer about 12.5 mg each, of USP Ketamine Hydrochloride RS and USP Ketamine Related Compound A RS, both accurately weighed, to a 50-mL volumetric flask, dissolve in *Mobile phase* with the aid of sonification if necessary, dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of the solution so obtained to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard preparation—Transfer about 10 mg of USP Ketamine Hydrochloride RS, accurately weighed, to a 50-mL volumetric flask, add about 20 mL of *Mobile phase,* and sonicate to dissolve. Dilute with *Mobile phase* to volume, and mix.

Assay preparation—Transfer about 20 mg of Ketamine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, add about 35 mL of *Mobile phase,* and sonicate to dissolve. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the order of elution is ketamine followed by ketamine related compound A; the resolution, *R,* between ketamine and ketamine related compound A is not less than ~~9.4;~~

■2.0;■1S (*USP27*)
the column efficiency determined from the ketamine peak is not less than 9400 theoretical plates; and the tailing factor determined from the ketamine peak is not more than 1.6. Chromatograph the *Standard preparation,* and record the ketamine peak response as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 0.6%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{13}H_{16}ClNO \cdot HCl$ in the portion of Ketamine Hydrochloride taken by the formula:

$$100C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Ketamine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the ketamine peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Ketorolac Tromethamine, *USP 26* page 1049—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40347-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Ketorolac Tromethamine RS.

Add the following:

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

BRIEFING

Labetalol Hydrochloride, *USP 26* page 1051 and page 1525 of *PF* 29(5) [Sept.–Oct. 2003]. It is proposed to clarify the relative standard deviation requirement in the test for *Diastereoisomer ratio.*

(PA5: A. Wilk) RTS—40325-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.* ■2S (*USP27*)
USP Labetalol Hydrochloride RS.

Change to read:

Diastereoisomer ratio—

1-Butaneboronic acid solution—Dissolve 1-butaneboronic acid in pyridine, previously dried over a suitable molecular sieve, and mix to obtain a solution having a known concentration of 20 mg per mL.

System suitability solution—Dissolve an accurately weighed quantity of USP Labetalol Hydrochloride RS in *1-Butaneboronic acid solution,* and dilute quantitatively and stepwise with *1-Butaneboronic acid solution* to obtain a solution having a known concentration of about 1.4 mg of USP Labetalol Hydrochloride RS per mL. Allow the solution to stand at room temperature for 20 minutes before using.

Test solution—Transfer about 1 mg of Labetalol Hydrochloride to a 1-mL reaction vial, add 0.7 mL of *1-Butaneboronic acid solution,* and mix until the labetalol hydrochloride is completely dissolved. Allow the solution to stand at room temperature for 20 minutes before using.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 2-mm × 1.8-m glass column packed with 10% phase G3 on 100- to 120-mesh support S1AB. The column is maintained at about 320°, and the injection port and the detector block are maintained at about 340°. Nitrogen is used as the carrier gas at the flow rate of about 30 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for the diastereoisomer B 1-butaneboronate derivative and 1.0 for the diastereoisomer A 1-butaneboronate derivative; the resolution, *R,* between the diastereoisomer A 1-butaneboronate derivative and diastereoisomer B 1-butaneboronate derivative peaks is not less than 1.5; and the relative standard deviation ■of the ratios of the peak areas of the diastereoisomers■2S (*USP27*) for replicate injections is not more than 2.0%.

Procedure—Inject about 2 µL of the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the diastereoisomer A content, in percentage, taken by the formula:

$$100 r_A / (r_A + r_B),$$

in which r_A is the peak area of the diastereoisomer A 1-butaneboronate derivative peak and r_B is the peak area of the diastereoisomer B 1-butaneboronate derivative peak. The diastereoisomer A content is not less than 45.0% and not more than 55.0%.

Add the following:

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

BRIEFING

Levorphanol Tartrate, *USP 26* page 1073—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40348-1)

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

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Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Levorphanol Tartrate RS.

Add the following:

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

BRIEFING

Lithium Carbonate Extended-Release Tablets, *USP 26* page 1089. It is proposed to add *Drug release Test 4* to this monograph because FDA recently approved a new generic version of this product that is bioequivalent to the Reference Listed Drug, but, due to differences in the formulation, requires a new drug release test. In the absence of any adverse comments, it is proposed to implement this revision via the *Second Interim Revision Announcement* pertaining to *USP 27–NF 22,* with an official date of April 1, 2004.

(BPC: M. Marques) RTS—40213-1; 40168-1

Change to read:

Drug release ⟨724⟩—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 1.*

Medium: dilute hydrochloric acid (7 in 1000); 800 mL.

Apparatus 1: 100 rpm.

Times: 15, 45, 90, and 120 minutes.

Procedure—At each *Time,* withdraw 8.0 mL of the solution under test, and pass through a filter having a 35-µm or finer porosity. Using the filtrate as the *Assay preparation,* suitably diluted with *Dissolution Medium* if necessary, and using *Dissolution Medium* to prepare the *Standard preparation,* determine the amount of Li_2CO_3 dissolved by employing a flame photometer, as directed in the *Assay.*

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 1.*

Time (minutes)	Amount dissolved
15	between 2% and 16%
45	between 25% and 45%
90	between 60% and 85%
120	not less than 85%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*

Apparatus and *Procedure*—Proceed as directed for *Test 1.*

Medium: water; 900 mL.

Times: 1, 3, and 7 hours.

Tolerances—The percentages of the labeled amount of Li_2Co_3 dissolved at the specified times conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	not more than 40%
3	between 45% and 75%
7	not less than 70%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3.*

Medium: water; 250 mL.

Apparatus 3: 6 dips per minute, 20-mesh top screen and 100-mesh bottom screen.

Procedure—Proceed as directed for *Test 1.*

Times and *Tolerances*—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 1.*

Time (hours)	Amount dissolved
1	between 10% and 45%
2	between 25% and 75%
6	not less than 70%

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

Medium, Apparatus, Times, and *Procedure*—Proceed as directed for *Test 1.*

Tolerances—The percentages of the labeled amount of Li_2CO_3 dissolved at the specified times conform to *Acceptance Table 1.*

Time (minutes)	Amount dissolved
15	between 2% and 16%
45	between 25% and 45%
90	between 60% and 85%
120	not less than 80% •2

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BRIEFING

Loperamide Hydrochloride Oral Solution, page 3101 of the *Second Supplement*. On the basis of comments received, it is proposed to change the range for *pH* to "between 2.7 and 6.5", because this range is representative of marketed products. In the absence of any adverse comment, it is proposed to implement this revision via the *First Interim Revision Announcement,* pertaining to *USP 27–NF 22*, with an official date of February 2, 2004. See also the briefing under *Dihydrotachysterol Oral Solution.*

(PA4: E. Gonikberg) RTS—40324-1; 40419-4

Change to read:

pH ⟨791⟩: between 2.7 and ~~5.0~~

•6.5.•(1)

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Lorazepam, *USP 26* page 1096—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-24

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Lorazepam RS. USP Lorazepam Related Compound A RS. USP Lorazepam Related Compound B RS.

Add the following:

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

BRIEFING

Magaldrate and Simethicone Tablets, *USP 26* page 1108. It is proposed to change the title of this monograph to *Magaldrate and Simethicone Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40430-1

Magaldrate and Simethicone Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Magaldrate and Simethicone Chewable Tablets**

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BRIEFING

Magaldrate and Simethicone Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40430-1

Add the following:

■Magaldrate and Simethicone Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Magaldrate and Simethicone Tablets)

» Magaldrate and Simethicone Chewable Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of magaldrate [$Al_5Mg_{10}(OH)_{31}(SO_4)_2$], and an amount of polydimethylsiloxane [$-(CH_3)_2SiO-]_n$ that is not less than 85.0 percent and not more than 115.0 percent of the labeled amount of simethicone.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label the Chewable Tablets to indicate that they are to be chewed before being swallowed.

USP Reference standards ⟨11⟩—*USP Magaldrate RS*. *USP Polydimethylsiloxane RS*.

Identification—

A: Transfer a quantity of powdered Chewable Tablets, equivalent to about 2 g of magaldrate, to a 100-mL centrifuge tube. Add about 60 mL of water, cap, and shake for 3 minutes. Centrifuge the suspension, and discard the supernatant. Repeat the washing with three more 60-mL portions of water. Transfer the residue to a 250-mL beaker, and heat on a steam bath to dryness: the residue so obtained meets the requirements of the *Identification* tests under *Magaldrate*.

B: The IR absorption spectrum, in the 7- to 11-μm region, determined in a 0.5-mm cell, of the *Assay preparation* prepared as directed in the *Assay for polydimethylsiloxane,* exhibits maxima only at the same wavelengths as that of the *Standard preparation* containing about 2 mg of USP Polydimethylsiloxane RS per mL prepared as directed in the *Assay for polydimethylsiloxane.*

Microbial limits ⟨61⟩—Chewable Tablets meet the requirements of the test for absence of *Escherichia coli*.

Uniformity of dosage units ⟨905⟩: meet the requirements for *Weight Variation* with respect to magaldrate.

Acid-neutralizing capacity—Proceed as directed under *Acid-neutralizing Capacity* ⟨301⟩. The acid consumed by the minimum single dose recommended in the labeling is not less than 5 mEq, and not less than the number of mEq calculated by the formula:

$$0.8(0.0282M),$$

in which 0.0282 is the theoretical acid-neutralizing capacity, in mEq per mg, of magaldrate, and M is the quantity, in mg, of the labeled amount of magaldrate.

Defoaming activity—

Foaming solution and *System suitability tests*—Proceed as directed in the test for *Defoaming activity* under *Magaldrate and Simethicone Oral Suspension*.

Procedure—[NOTE—For each test use a clean 250-mL cylindrical jar (50-mm internal diameter × 110-mm internal height) with a 50-mm opening fitted with a tight cap with an inert liner.] Transfer a quantity of finely powdered Chewable Tablets, equivalent to 20 mg of simethicone, to a 250-mL cylindrical jar containing 50 mL of 0.6 N hydrochloric acid that has been warmed to 37°, and proceed as directed in the test for *Defoaming activity* under *Magaldrate and Simethicone Oral Suspension,* beginning with ‘‘Cap the jar.’’ Record the time, in seconds, for the foam to collapse

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to the extent that its thickness, measured from the surface of the liquid, is 1.0 cm. The defoaming activity time does not exceed 45 seconds.

Magnesium hydroxide content—

Test preparation—Weigh and finely powder not less than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 1 g of magaldrate, to a 100-mL volumetric flask, add 30 mL of dilute hydrochloric acid (1 in 10), shake for 15 minutes, dilute with water to volume, and mix.

Procedure—Transfer 10.0 mL of *Test preparation* to a 400-mL beaker, and proceed as directed in the test for *Magnesium hydroxide content* under *Magaldrate,* beginning with "and dilute with water to about 200 mL." Not less than 492 mg and not more than 666 mg of magnesium hydroxide [$Mg(OH)_2$] per g of the labeled amount of magaldrate is found.

Aluminum hydroxide content—

Edetate disodium titrant—Prepare and standardize as directed in the *Assay* under *Ammonium Alum*.

Test preparation—Prepare as directed in the test for *Magnesium hydroxide content*.

Procedure—Transfer 10.0 mL of *Test preparation* and 20 mL of water to a 250-mL beaker, and proceed as directed for *Procedure* in the test for *Aluminum hydroxide content* under *Magaldrate*, beginning with "Add, with stirring, 25.0 mL of *Edetate disodium*." Not less than 321 mg and not more than 459 mg of aluminum hydroxide [$Al(OH)_3$] per g of the labeled amount of magaldrate is found.

Assay for magaldrate—Weigh and finely powder not less than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 6 g of magaldrate, to a 200-mL volumetric flask. Add 100.0 mL of 2 N hydrochloric acid VS, and swirl by mechanical means for 30 minutes. Dilute with water to volume, mix, and filter. Transfer 100.0 mL of the filtrate to a beaker. Titrate the excess acid with 1 N sodium hydroxide VS to a pH of 3.0, determined potentiometrically. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩). Each mL of 2 N hydrochloric acid is equivalent to 70.80 mg of $Al_5Mg_{10}(OH)_{31}(SO_4)_2$.

Assay for polydimethylsiloxane—Weigh and finely powder not less than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 20 mg of simethicone, to a 60-mL separator. Add 10.0 mL of hexanes and 25 mL of 6 N hydrochloric acid, cap the separator, and shake by mechanical means for not less than 2 hours. Allow to stand for about 10 minutes, and drain off as much of the lower, aqueous layer as possible without removing any of the unseparated interphase. Add 25 mL of 4 N sodium hydroxide to the separator, cap it, and shake by mechanical means for 1 hour. Transfer the mixture from the separator to a 50-mL centrifuge tube, cap, and centrifuge to obtain clear layers. Transfer not less than 5 mL of the clear upper hexanes layer to a test tube containing about 0.5 g of anhydrous sodium sulfate. Cap the tube, shake vigorously, and allow to stand to obtain a clear supernatant (*Assay preparation*). Prepare three *Standard preparations* in hexanes having known concentrations of about 1.6, 2.0, and 2.4 mg of USP Polydimethylsiloxane RS per mL, respectively. Concomitantly determine the absorbances of the *Assay preparation* and the *Standard preparations* in a 0.5-mm cell at the wavelength of maximum absorbance at about 1260 cm^{-1} with an IR spectrophotometer, using hexanes as the blank. [NOTE—Between each measurement, rinse the cell with heptane, empty, and dry it.] Plot the absorbances for the *Standard preparations* versus concentration, in mg per mL, of USP Polydimethylsiloxane RS, and draw the straight line best fitting the three plotted points. From the graph so obtained, determine the concentration, *C,*

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in mg per mL, of polydimethylsiloxane in the *Assay preparation.* Calculate the quantity, in mg, of $[-(CH_3)_2SiO-]_n$ in the portion of Chewable Tablets taken by multiplying *C* by 10.■2S (*USP27*)

(Official February 1, 2007)

BRIEFING

Magnesium Sulfate, *USP 26* page 1118—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado) RTS—40364-25

Change to read:

Labeling—The label states whether it is the monohydrate, the dried form, or the heptahydrate. Magnesium Sulfate intended for use in preparing parenteral dosage forms is so labeled. Magnesium Sulfate not intended for use in preparing parenteral dosage forms is so labeled; in addition, it may be labeled also as intended for use in preparing nonparenteral dosage forms.

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

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

BRIEFING

Mangafodipir Trisodium, *USP 26* page 1121 and page 1047 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-17

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

Related compounds—

Ascorbic acid solution—Dissolve 0.4 g of ascorbic acid in 100 mL of water.

Phosphate buffer—Prepare as directed in the *Assay.*

Mobile phase—Prepare as directed in the *Assay.* [NOTE—Increasing the proportion of acetonitrile will decrease the retention times.]

System suitability stock solution—Prepare as directed for *Standard stock preparation* in the *Assay.*

System suitability solution 1—Prepare a solution of USP Mangafodipir Trisodium RS having a known concentration of about 4.0 mg per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, add 5.0 mL of *System suitability stock solution,* 5.0 mL of *Phosphate buffer,* and 5.0 mL of *Ascorbic acid solution.* Dilute with nitrogen-purged water to volume, and mix to obtain a solution having a concentration of about 0.4 mg of USP Mangafodipir Trisodium RS, and about 0.01 mg each of USP Mangafodipir Related Compound A RS and USP Mangafodipir Related Compound B RS per mL. [NOTE—Store in a refrigerator and under nitrogen to avoid excessive exposure to heat, air, and light.]

System suitability solution 2—Transfer about 10 mg of USP Mangafodipir Related Compound C RS to a 100-mL volumetric flask, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, and add 5.0 mL of *Phosphate buffer.*

Test solution—Transfer an accurately weighed quantity of Mangafodipir Trisodium, equivalent to about 100 mg of mangafodipir trisodium, to a 50-mL volumetric flask, dilute with water to volume, and mix. Transfer 10.0 mL of this solution to a second 50-mL volumetric flask, add 5.0 mL of *Phosphate buffer*, dilute with water to volume, and mix. [NOTE—Store in a refrigerator and under nitrogen to avoid excessive exposure to heat, air, and light.]

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay.* Chromatograph *System suitability solution 2,* and record the peak responses as directed for *Procedure:* note the elution time to identify the mangafodipir related compound C peak, if present, in the chromatogram of *System suitability solution 1.* Chromatograph *System suitability solution 1,* and record the peak responses as directed for *Procedure:* the reten-

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tion time for mangafodipir is between 18 and 30 minutes. The peak area for mangafodipir related compound C is less than 0.1%. [NOTE—If the peak area is more than 0.1% of the total of all peak areas, prepare fresh quantities of *Ascorbic acid solution* and *System suitability solution 1,* and repeat the test. If the peak area of mangafodipir related compound C is still greater than 0.1%, repeat the test using another column. A contaminated column can result in oxidation of Mn(II) to Mn(III), forming related compound C.] The tailing factor for the mangafodipir peak is not more than 2.3; the column efficiency is not less than 1000 theoretical plates; the resolution, *R,* between mangafodipir related compound B and mangafodipir is not less than 1.5; and the relative standard deviation for replicate injections is not more than 10% for each peak. [NOTE—If the resolution is less than 1.5, adjust the *Mobile phase* by increasing the concentration of tetrabutylammonium hydrogen sulfate.]

Procedure—Inject about 10 µL of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for all of the major peaks. The relative retention times for ascorbic acid, mangafodipir related compound A, Mn(II)-5-methyl dipyridoxal monophosphate (Mn(II)-5-methyl DPMP) if present, mangafodipir related compound C, mangafodipir related compound B, and mangafodipir are about 0.1, 0.3, 0.4, 0.6, 0.8, and 1.0, respectively. Calculate the percentages of mangafodipir related compound A, mangafodipir related compound B, mangafodipir related compound C, and Mn(II)-5-methyl DPMP in the portion of Mangafodipir Trisodium taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak area of each impurity; and r_s is the sum of the areas of all of the peaks: not more than 0.5% each of mangafodipir related compound A and mangafodipir related compound B is found; not more than 0.6% of mangafodipir related compound C is found; not more than 0.3% of Mn(II)-5-methyl DPMP is found; not more than ~~0.1%~~

■0.3%■1S (*USP27*)
of any other impurity is found; ~~and~~

■■1S (*USP27*)
not more than a total of 0.5% of other impurities is found;

■and not more than 2.0% of total impurities is found.■1S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Mangafodipir Trisodium is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Manganese Chloride for Oral Solution, *USP 26* page 1124—See briefing under *Ferric Ammonium Citrate for Oral Solution.*

(RMI: A. Wilk) RTS—40369-4

Add the following:

■**Uniformity of dosage units** ⟨905⟩—FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Manganese Sulfate, *USP 26* page 1125—See briefing under *Acepromazine Maleate.*

(VET: I. DeVeau; PSD: C. Okeke) RTS—40270-13

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**USP Reference standards** ⟨11⟩—*USP Endotoxin RS.*■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Manganese Sulfate is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Manganese Sulfate Injection*. Where the label states that Manganese Sulfate must be subjected to further processing during the preparation

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of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Manganese Sulfate Injection*.■2S (*USP27*)

BRIEFING

Mebrofenin, *USP 26* page 1133—See briefing under *Adenosine*.

(RMI: A. Wilk) RTS—40329-18

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Mebrofenin RS.

Add the following:

■**Other requirements—**Where the label states that Mebrofenin is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Sodium Pertechnetate Tc 99m Injection*. Where the label states that Mebrofenin must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Sodium Pertechnetate Tc 99m Injection*.■2S (*USP27*)

BRIEFING

Menotropins, *USP 26* page 1148 and page 1532 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Acepromazine Maleate*. In addition, minor editorial style changes have been made.

(BNT: I. DeVeau) RTS—40270-14

Add the following:

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

Change to read:

USP Reference standards ⟨**11**⟩—~~*USP Chorionic Gonadotropin RS*~~.

■*USP Human Chorionic Gonadotropin RS.*■2S (*USP27*)
USP Endotoxin RS. USP Menotropins RS.

Add the following:

■**Other requirements—**Where the label states that Menotropins is sterile, it meets the requirements for *Sterility* under *Menotropins for Injection*.■2S (*USP27*)

Change to read:

Assay for follicle-stimulating hormone—

Diluting solution—Using the *Diluent* under *Assay for luteinizing hormone,* dissolve an accurately weighed quantity of ~~USP Chorionic Gonadotropin RS~~

■USP Human Chorionic Gonadotropin RS■2S (*USP27*) to obtain a solution having a concentration of 70 USP Chorionic Gonadotropin Units per mL, readjusting the pH, if necessary, to 7.2 ± 0.2.

Standard preparations—Dissolve an accurately weighed quantity of USP Menotropins RS in the *Diluting solution* to obtain solutions having known concentrations of about 2.5, 5.0, and 10.0 USP Follicle-Stimulating Hormone Units per mL.

Assay preparations—Following the procedure given under the *Standard preparations,* use Menotropins in place of the Reference Standard to obtain similar solutions.

Control solution—Use the *Diluting solution* as the control solution. Store all solutions at 5 ± 3° for the duration of the assay, and properly dispose of any unused portions.

Test animals—Select 20- to 21-day old female rats with weights within a 10-g range of each other. Proceed as directed under *Test animals* in the *Assay for luteinizing hormone* beginning with "House the animals."

Dose determination trial—Use the method described under *Procedure* to determine a 3-dose range in which the lowest dose produces a definite response in some of the rats in the low-dose group (as compared with the control group) and the highest dose produces a submaximal to maximal response in the high-dose group. Doses must be established in a geometric progression. The normal dose response range will occur between 0.5 and 6.0 USP Follicle-Stimulating Hormone Units total dose per rat. Useful dose ranges will vary with the sensitivity of the rat strain selected.

Procedure—Inject each rat of each group subcutaneously in the dorsal area with 0.2 mL of the solution to which it was assigned. For *Dose determination trial* only, similarly inject each rat in the control group with 0.2 mL of the *Control solution.* Repeat these injections at approximately the same time of day after 24 hours and 48 hours. Twenty-four hours after the last injection, weigh each rat, sacrifice the animals, and carefully dissect out the ovaries of each rat, removing any fat and fibrous tissue. Thoroughly dry the ovaries by pressing against absorbent paper, avoiding damage to follicles on the ovary surface, and immediately weigh them to the nearest 0.2 mg, using a suitable balance.

Calculation—Tabulate the observed ovarian pair weight for each rat designated by the symbol *y*, for each dosage group of *f* rats. For apparently outlying ovarian weight gain, an attempt may be made to correct the organ mass relative to the mass of the rat from which it was taken. For the *y*-value in question, calculate for each of the *f* rats in the appropriate group the ratio of ovarian weight to the total body weight. Reject the *y*-value if its corresponding ratio differs from the rest of the group by more than 1.5 standard deviations. If the data from one or more rats are missing, adjust to groups of equal size by suitable means (see *Replacement of Missing Values* under *Design and Analysis of Biological Assays* ⟨111⟩). Total the values of *y* in each group, and designate each total as *T,* using subscripts 1 to 3 for the three successive dosage levels and subscripts *S* and *U* for the Standard and the material under test, respectively. Test both the agreement in slope of the dosage-response lines for the Standard and for the material under test, and the lack of curvature as directed for a 3-dose balanced assay (see *Tests of Assay Validity* under general chapter ⟨111⟩). If the combined discrepancy as measured by F_3 exceeds its tabular value in *Table 9* (see *Combination of Independent Assays* under general chapter ⟨111⟩), regard these data as preliminary, and repeat the assay.

Determine the logarithm of follicle-stimulating hormone potency of the Menotropins taken by the formula:

$$M = (4iT_a / 3T_b) + \log R,$$

in which $T_a = \Sigma(T_U - T_S)$; $T_b = \Sigma(T_3 - T_1)$; *i* is the interval between successive log doses of both the *Standard preparation* and *Assay preparation;* and $R = v_S / v_U$ is the ratio of the high dose of the Standard in USP Units (v_S) to the high dose of the Menotropins in mg (v_U). Compute the log confidence interval (see *Design and Analysis of Biological Assays* ⟨111⟩).

Replication—Repeat the entire determination at least once. Test the agreement among the two or more independent determinations, and compute the weights/mean log-potency *M* and its confidence interval, L_C (see *Confidence Intervals for Individual Assays* under general chapter ⟨111⟩). If this exceeds 0.18, repeat the assay until the confidence interval of the combined results is 0.18 or less.

The potency P_* is satisfactory if P_* = antilog *M* is not less than 80% and not more than 125% of the labeled potency and if the log confidence interval does not exceed 0.18.

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BRIEFING

Meperidine Hydrochloride, *USP 26* page 1151—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40349-1

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Meperidine Hydrochloride RS.

Add the following:

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

BRIEFING

Meprobamate Oral Suspension, *USP 26* page 1157—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-9

Add the following:

■**Uniformity of dosage units** ⟨905⟩**—**

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Mesoridazine Besylate, *USP 26* page 1166—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-26

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Mesoridazine Besylate RS.

Add the following:

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

BRIEFING

Mesoridazine Besylate Oral Solution, *USP 26* page 1167—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-10

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

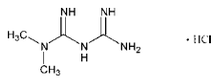
BRIEFING

Metformin Hydrochloride; Metformin Hydrochloride Tablets. Because there are no existing *USP* monographs for this drug substance, new monographs are being proposed. The liquid chromatographic procedure in the test for *Related compounds* is based on analyses performed with the Partisil SCX brand of L9 column. The typical retention times at a flow rate of 1.7 mL per minute are about 2 minutes for metformin related compound A, about 3 minutes for melamine, and about 10 to 12 minutes for metformin.

(PA4: E. Gonikberg) RTS—34256-1

Add the following:

■Metformin Hydrochloride



$C_4H_{11}N_5 \cdot HCl$ 165.62

Imidodicarbonimidic diamide, *N,N*-dimethyl-, monohydrochloride.

1,1-Dimethylbiguanide monohydrochloride [*1115-70-4*].

» Metformin Hydrochloride contains not less than 98.5 percent and not more than 101.0 percent of $C_4H_{11}N_5 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

USP Reference standards ⟨11⟩—*USP Metformin Hydrochloride RS. USP Metformin Related Compound A RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

B: It meets the requirements of the tests for *Chloride* ⟨191⟩.

Loss on drying ⟨731⟩—Dry it at 105° for 5 hours: it loses not more than 0.5% of its weight.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method I* ⟨231⟩: 0.001%.

Related compounds—

Mobile phase—Prepare a solution in water, containing 17 g of monobasic ammonium phosphate per L, adjust with phosphoric acid to a pH of 3.0, and mix.

Standard solution—Prepare a solution of USP Metformin Related Compound A RS in water having a known concentration of about 0.2 mg per mL. Transfer 1.0 mL of this solution to a 200-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. [NOTE—Metformin related compound A is 1-cyanoguanidine.]

Test solution—Transfer about 500 mg of Metformin Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Diluted test solution—Transfer 1.0 mL of the *Test solution* to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Resolution solution—Transfer about 10 mg of melamine to a 100-mL volumetric flask, and dissolve in about 90 mL of water. Add 5.0 mL of the *Test solution,* dilute with water to volume, and mix. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 218-nm detector and a 4.6-mm × 25-cm column containing packing L9. The flow rate is about 1.0 to 1.7 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between melamine and metformin is not less than 10.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution,* the *Standard solution,* and the *Diluted test solution* into the chromatograph, record the chromatograms for not less than twice the retention time of metformin, and measure the peak areas. The area of a peak corresponding to metformin related compound A in the chromatogram of the *Test solution* is not greater than the

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area of the corresponding peak in the chromatogram of the *Standard solution:* not more than 0.02% of metformin related compound A is found.

The area of any other secondary peak in the chromatogram of the *Test solution* is not greater than the area of the major peak in the chromatogram of the *Diluted test solution;* and the sum of the areas of all secondary peaks in the chromatogram of the *Test solution* is not greater than five times the area of the major peak in the chromatogram of the *Diluted test solution:* not more than 0.1% of any other impurity is found; and not more than 0.5% of total impurities is found.

Assay—[NOTE—To avoid overheating of the reaction medium, mix thoroughly throughout the titration, and stop the titration immediately after the endpoint has been reached.] Dissolve about 60 mg of Metformin Hydrochloride, accurately weighed, in 4 mL of anhydrous formic acid. Add 50 mL of acetic anhydride. Titrate with 0.1 N perchloric acid VS, determining the endpoint potentiometrically. Perform a blank determination, and make any necessary correction (see *Titrimetry* ⟨541⟩). Each mL of 0.1 N perchloric acid is equivalent to 8.28 mg of $C_4H_{11}N_5 \cdot HCl$.■2S (*USP27*)

BRIEFING

Metformin Hydrochloride Tablets—See briefing under *Metformin Hydrochloride*. It is proposed to have two different *Dissolution* tests: *Test 1* for all approved ANDA and *Test 2* for the Reference Listed Drug.

(PA4: E. Gonikberg; BPC: M. Marques) RTS—34256-2; 40422-2

Add the following:

■Metformin Hydrochloride Tablets

» Metformin Hydrochloride Tablets contain not less than 95.0 percent and not more than 105.0 percent of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$).

Packaging and storage—Preserve in tight containers. Store at controlled room temperature.

Labeling—When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

USP Reference standards ⟨11⟩—*USP Metformin Hydrochloride RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

Test specimen—Transfer a quantity of powdered Tablets, equivalent to about 20 mg of metformin hydrochloride, to a suitable flask, add 20 mL of dehydrated alcohol, and shake. Filter, evaporate the filtrate on a water bath to dryness, and dry the residue at 105° for 1 hour.

B: Triturate a quantity of the powdered Tablets, equivalent to about 50 mg of metformin hydrochloride, with 10 mL of water, and filter. To 5 mL of the filtrate add 1.5 mL of 5 N sodium hydroxide solution and 1 mL of a 1-napthol solution, prepared by dissolving 1 g of 1-naphthol in a solution containing 6 g of sodium hydroxide and 16 g of anhydrous sodium carbonate in 100 mL of water. Add 0.5 mL of sodium hypochlorite TS, dropwise, and with shaking: an orange-red color is produced that darkens on standing.

C: Triturate a quantity of the powdered Tablets, equivalent to about 50 mg of metformin hydrochloride, with 10 mL of water, and filter. The filtrate meets the requirements of the tests for *Chloride* ⟨191⟩.

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Dissolution ⟨711⟩—

TEST 1 —

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 100 rpm.

Time: 45 minutes.

Procedure—Determine the amount of $C_4H_{11}N_5 \cdot HCl$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 233 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium*, if necessary, in comparison with a Standard solution having a known concentration of USP Metformin Hydrochloride RS in the same *Medium.*

Tolerances—Not less than 70% (*Q*) of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 45 minutes.

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2.*

For products labeled to contain 500 mg of Metformin—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 50 rpm.

Time: 30 minutes.

Procedure—Proceed as directed under *Test 1.*

Tolerances—Not less than 80% (*Q*) of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 minutes.

For products labeled to contain 850 mg or 1000 mg of Metformin—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 75 rpm.

Time: 30 minutes.

Procedure—Proceed as directed under *Test 1.*

Tolerances—Not less than 75% (*Q*) of the labeled amount of $C_4H_{11}N_5 \cdot HCl$ is dissolved in 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Related compounds—

Mobile phase, Resolution solution, Diluted test solution, and *Chromatographic system*—Proceed as directed in the test for *Related compounds* under *Metformin Hydrochloride*.

Test solution—Weigh and finely powder not fewer than 20 Tablets. Transfer a portion of the powder, equivalent to about 500 mg of metformin hydrochloride, to a 100-mL volumetric flask, dissolve in *Mobile phase,* with shaking, dilute with *Mobile phase* to volume, and mix. Filter, and use the filtrate.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Diluted test solution* into the chromatograph, record the chromatograms for not less than twice the retention time of metformin, and measure the peak areas.

The area of any secondary peak in the chromatogram of the *Test solution* is not greater than the area of the major peak in the chromatogram of the *Diluted test solution;* and the sum of the areas of all secondary peaks in the chromatogram of the *Test solution* is not greater than five times the area of the major peak in the chromatogram of the *Diluted test solution:* not more than 0.1% of any impurity is found; and not more than 0.5% of total impurities is found.

Assay—

Standard preparation—Prepare a solution of USP Metformin Hydrochloride RS in water having a known concentration of about 10 µg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 100 mg of metformin hydrochloride, to a 100-mL volumetric flask. Add 70 mL of water, shake by mechanical means for 15 minutes, dilute with water to volume, and filter, discarding the first 20 mL

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of the filtrate. Dilute 10.0 mL of the filtrate with water to 100.0 mL, and dilute 10.0 mL of the resulting solution with water to 100.0 mL.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Assay preparation,* in 1-cm cells, at the wavelength of maximum absorbance at about 232 nm, with a suitable spectrophotometer, using water as a blank. Calculate the quantity, in mg, of metformin hydrochloride ($C_4H_{11}N_5 \cdot HCl$) in the portion of Tablets taken by the formula:

$$10C(A_U / A_S),$$

in which C is the concentration, in µg per mL, of USP Metformin Hydrochloride RS in the *Standard preparation;* and A_U and A_S are the absorbances obtained from the *Standard preparation* and the *Assay preparation,* respectively.■2S (*USP27*)

BRIEFING

Methadone Hydrochloride, *USP 26* page 1175—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40350-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Methadone Hydrochloride RS.

Add the following:

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

BRIEFING

Methenamine Elixir, *USP 26* page 1182—See briefing under *Acyclovir Oral Suspension.*

(PA7b: B. Davani) RTS—40396-3

Methenamine Elixir

(Current title—not to change until June 1, 2005)
Monograph title change—to become official June 1, 2005
***See* Methenamine Oral Solution**

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ELIXIR PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ELIXIR PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

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BRIEFING

Methenamine Mandelate for Oral Solution, *USP 26* page 1184—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40396-5

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR POWDER PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩

FOR POWDER PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Methenamine Mandelate Oral Suspension, *USP 26* page 1185—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40396-4

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Methenamine Oral Solution, *USP 26* page 1183—See briefing under *Acyclovir Oral Suspension.*

(PA7b: B. Davani) RTS—40400-1

Methenamine Oral Solution

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

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Methocarbamol, *USP 26* page 1187—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-27

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

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Change to read:
USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Guaifenesin RS. USP Methocarbamol RS.

Add the following:

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

Change to read:
USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Methotrimeprazine RS.

Add the following:

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

BRIEFING

Methotrimeprazine, *USP 26* page 1191—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40351-1

BRIEFING

Methyldopa Oral Suspension, *USP 26* page 1200—See briefing under *Chlorothiazide Oral Suspension.*

(PA5: A. Wilk) RTS—40368-5

Change to read:
Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Methylphenidate Hydrochloride, *USP 26* page 1208. It is proposed to replace the use of USP Methylphenidate Hydrochloride Erythro Isomer RS by USP Methylphenidate Hydrochloride Erythro Isomer Solution RS that will soon become available. The changes in the test for *Limit of erythro* [*(R*, S*)*] are to accommodate the use of this Reference Standard.

(PA3: S. Salado) RTS—40415-1

Change to read:

USP Reference standards ⟨11⟩—*USP Methylphenidate Hydrochloride RS.* ~~*USP Methylphenidate Hydrochloride Erythro Isomer RS.*~~

■*USP Methylphenidate Hydrochloride Erythro Isomer Solution RS.*■2S (*USP27*)
USP α-Phenyl-2-piperidineacetic Acid Hydrochloride RS.

Change to read:

Limit of erythro [*(R*, S*)*] isomer—
Mobile solvent—Prepare a solution consisting of a mixture of chloroform, methanol, and ammonium hydroxide (190:10:1).
Detecting reagent—Dissolve 0.7 g of bismuth subnitrate in 40 mL of a mixture of water and glacial acetic acid (4:1). Add 40 mL of potassium iodide solution (2 in 5), then add 120 mL of glacial acetic acid and 250 mL of water.

■*Test solution*—Prepare a solution in methanol containing 50 mg of Methylphenidate Hydrochloride per mL.■2S (*USP27*)
Procedure—~~Prepare methanol solutions of Methylphenidate Hydrochloride and of USP Methylphenidate Hydrochloride Erythro Isomer RS containing 50 mg per mL and 0.5 mg per mL, respectively. Apply 20 µL portions of each solution~~

■Apply 20-µL portions of the *Test solution* and USP Methylphenidate Hydrochloride Erythro Isomer Solution RS■2S (*USP27*)
to a suitable thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel. Allow the spots to dry, and develop the chromatogram, using the *Mobile solvent,* in a suitable chamber, lined with absorbent paper and previously equilibrated with the *Mobile solvent,* until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the developing chamber, and allow the solvent to evaporate. Locate the spots on the plate by spraying first with the *Detecting reagent* and then with 1 N sulfuric acid. Any spot in the lane from the methylphenidate hydrochloride at the same R_F as the erythro isomer is not larger or more intense than that produced by ~~USP Methylphenidate Hydrochloride Erythro Isomer RS,~~

■USP Methylphenidate Hydrochloride Erythro Isomer Solution RS,■2S (*USP27*)
when viewed under ordinary lighting (1%).

BRIEFING

Metoclopramide Oral Solution, *USP 26* page 1218—See briefing under *Dihydrotachysterol Oral Solution.*

(PA4: E. Gonikberg) RTS—40419-5

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩ —

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Metolazone Tablets, *USP 26* page 1220. On the basis of data received, it is proposed to change the procedure in the *Assay* from a spectrophotometric measurement to HPLC. The proposed method was validated using the Waters, Symmetry C-18 brand of L1 packing. The typical retention time for metolazone is 10.3 minutes. It is also proposed to revise the *Packaging and storage* section.

(PA5: A. Wilk) RTS—39659-1

Change to read:

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

■and store below 30°.■2S (*USP27*)

Change to read:

Assay—[NOTE—Use low-actinic glassware throughout the *Assay.*]
~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Metolazone RS in alcohol to obtain a solution having a known concentration of about 40 µg per mL.~~
~~*Assay preparation*—Weigh and finely powder not less than 20 Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 40 mg of metolazone, to a 250-mL volumetric~~

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~~flask, add 150 mL of alcohol, sonicate for 2 minutes, dilute with alcohol to volume, and filter. Pipet 25 mL of the filtrate into a 100-mL volumetric flask, dilute with alcohol to volume, and mix.~~

~~*Procedure*—Concomitantly determine the absorbances of the solutions at the wavelength of maximum absorbance at about 343 nm, with a suitable spectrophotometer, using alcohol as the blank. Calculate the quantity, in mg, of $C_{16}H_{16}ClN_3O_3S$ in the portion of Tablets taken by the formula:~~

~~$$C(A_U/A_S),$$~~

~~in which *C* is the concentration, in µg per mL, of USP Metolazone RS in the *Standard preparation*, and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation*, respectively.~~

■*Mobile phase*—Dissolve 1.38 g of monobasic potassium phosphate monohydrate in about 900 mL of water, adjust with phosphoric acid to a pH of 3.0, and dilute with water to 1000 mL. Prepare a filtered and degassed mixture of this buffer solution, methanol, and acetonitrile (65:28:7). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Metolazone RS in methanol to obtain a solution having a known concentration of about 5 µg per mL.

Assay preparation—Transfer 10 Tablets to a 200-mL volumetric flask, add 3 mL of water and about 100 mL of methanol. Sonicate for 30 minutes. If disintegration is not complete, sonicate for an additional 30 minutes. Shake by mechanical means for about 30 minutes. Dilute with methanol to volume, and mix. Transfer an accurately measured volume of this stock solution, equivalent to about 0.25 mg of metolazone, to a 50-mL volumetric flask, dilute with methanol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.1 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not less than 2.0%.

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the metolazone peak. Calculate the quantity, in mg, of $C_{16}H_{16}ClN_3O_3S$ in the portion of Metolazone Tablets taken by the formula:

$$50C(r_U/r_S),$$

in which *C* is the concentration, in mg per mL, of USP Metolazone RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Metronidazole, *USP 26* page 1226—See briefing under *Acyclovir.*

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-12

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Metronidazole RS.*

■*USP Endotoxin RS.*■2S (*USP27*)

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Add the following:

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

BRIEFING

Miconazole, *USP 26* page 1234—See briefing under *Acyclovir.*

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-13

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Miconazole RS.

Add the following:

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

BRIEFING

Morphine Sulfate, *USP 26* page 1254—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40352-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Morphine Sulfate RS.

Add the following:

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

In-Process Revision

BRIEFING

Nalidixic Acid Oral Suspension, *USP 26* page 1265. It is proposed to correct a typographical error in the volume of methanol added in the preparation of the *Mobile phase* in the *Assay.* In addition, minor editorial style changes have been made. In the absence of any significant adverse comments, it is proposed to implement the revision in the *Assay* via the *Second Interim Revision Announcement* pertaining to *USP 27–NF 22,* with an official date of April 1, 2004. See also the briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40283-1; 40399-1

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Change to read:

Assay—

Mobile phase—Prepare a solution of 784 mg of dibasic potassium phosphate in 325 mL of water. To this solution add a solution of 2.62 g of hexadecyltrimethylammonium bromide in 350 mL of methanol. To the combined solution add ~~25 mL~~ •325 mL•2 of methanol, mix, filter, and degas. This solution has an apparent pH of about 10. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard solution—Prepare a solution of sulfanilic acid in *Mobile phase* containing about 0.8 mg per mL.

Standard preparation—Prepare a solution having a known concentration of about 0.18 mg per mL of USP Nalidixic Acid RS in methanol. Transfer 5.0 mL of this solution and 1.0 mL of *Internal standard solution* to a 25-mL volumetric flask, dilute with methanol to volume, and mix.

Assay preparation—Transfer an accurately measured volume of freshly mixed Oral Suspension, equivalent to about 150 mg of nalidixic acid, to a 500-mL volumetric flask, add about 400 mL of methanol, and sonicate for about 30 minutes. Shake by mechanical means for about 30 minutes, sonicate again for about 30 minutes, dilute with methanol to volume, mix, and filter. Transfer 3.0 mL of the clear filtrate and 1.0 mL of *Internal standard solution* to a 25-mL volumetric flask, dilute with methanol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.7 for sulfanilic acid and 1.0 for nalidixic acid; the resolution, *R,* between sulfanilic acid and nalidixic acid is not less than 1; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure— Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{12}H_{12}N_2O_3$ in each mL of the Oral Suspension taken by the formula:

$$(12{,}500/3)(C/V)(R_U/R_S),$$

in which C is the concentration, in mg per mL, of USP Nalidixic Acid RS in the *Standard preparation; V* is the volume, in mL, of Oral Suspension taken to prepare the *Assay preparation;* and R_U and R_S are the ratios of the peak areas for nalidixic acid and sulfanilic acid in the chromatograms obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Nalorphine Hydrochloride, *USP 26* page 1266—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40353-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Nalorphine Hydrochloride RS.

Add the following:

■**Other requirements—**Where the label states that Nalorphine Hydrochloride is sterile, it meets the requirements for *Sterility* and *Bacterial endotoxins* under *Nalorphine*

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Hydrochloride Injection. Where the label states that Nalorphine Hydrochloride must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Bacterial endotoxins* under *Nalorphine Hydrochloride Injection.* ■2S (*USP27*)

BRIEFING

Naloxone Hydrochloride, *USP 26* page 1267—See briefing under *Alfentanil Hydrochloride*.

(PA2: C. Anthony; PSD: C. Okeke) RTS—40354-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Naloxone RS. USP Noroxymorphone Hydrochloride RS.

Add the following:

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

BRIEFING

Neostigmine Methylsulfate, *USP 26* page 1303—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-28

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

■**Other requirements—**Where the label states that Neostigmine Methylsulfate is sterile, it meets the requirements for *Sterility* under *Neostigmine Methylsulfate Injection.*■2S (*USP27*)

In-Process Revision

BRIEFING

Niacin, *USP 26* page 1304 and page 1056 of *PF* 29(4) [July–Aug. 2003]. It is proposed to delete the *Test preparation* in the test for *Organic volatile impurities* to eliminate inconsistency with the preparation of the *Standard Solution* as specified in the general test chapter under *Method IV.*

(DSN: L. Evans) RTS—40363-1

Change to read:

Identification—
A: *Infrared Absorption* ⟨197M⟩.
B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 20 µg per mL.
Medium: ~~water.~~

■Use the *Buffer solution,* prepared as directed in the *Assay.*■1S (*USP27*)
Ratio: A_{237}/A_{262}, between ~~0.35 and 0.39.~~

■0.46 and 0.50.■1S (*USP27*)

Change to read:

Organic volatile impurities, *Method IV* ⟨467⟩: meets the requirements.
~~*Test preparation*—Transfer 100 mg of Niacin to a vial, add 5 mL water, seal the vial, and heat to 80° for 60 minutes.~~

■■2S (*USP27*)

Change to read:

Assay—~~Transfer about 200 mg of Niacin, accurately weighed, to a 500-mL volumetric flask, add water to dissolve, dilute with water to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with water to volume, and mix. Concomitantly determine the absorbances of this solution and a solution of USP Niacin RS in the same medium, at a concentration of about 20 µg per mL, in 1-cm cells at the wavelength of maximum absorbance at about 262 nm, with a suitable spectrophotometer, using water as the blank. Calculate the quantity, in mg, of $C_6H_5NO_2$ in the Niacin taken by the formula:~~

~~$10C(A_U/A_S)$,~~

~~in which C is the concentration, in µg per mL, of USP Niacin RS in the Standard solution, and A_U and A_S are the absorbances of the solution of Niacin and the Standard solution, respectively.~~

■*Buffer solution*—Dissolve 6.8 g of monobasic potassium phosphate in 1 L of water. Adjust with 50% sodium hydroxide solution to a pH of 7.0.

Assay preparation—Transfer about 200 mg of Niacin, accurately weighed, to a 500-mL volumetric flask, add the *Buffer solution* to dissolve, dilute with the *Buffer solution* to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with the *Buffer solution* to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Assay preparation* and a solution of USP Niacin RS in the same medium *(Standard preparation),* at a concentration of about 20 µg per mL, in 1-cm cells at the wavelength of maximum absorbance at about 262 nm, with a suitable spectrophotometer, using the *Buffer solution* as the blank. Calculate the quantity, in mg, of $C_6H_5NO_2$ in the portion of Niacin taken by the formula:

$$10C(A_U/A_S),$$

in which C is the concentration, in µg per mL, of USP Niacin RS in the *Standard preparation;* and A_U and A_S are the absorbances of the solution of the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP27*)

BRIEFING

Nitrofurantoin Oral Suspension, *USP 26* page 1316—See briefing under *Acyclovir Oral Suspension.*

(PA7b: B. Davani) RTS—40399-2

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

In-Process Revision

BRIEFING

Nitrofurazone, *USP 26* page 1317. In accordance with the implemented name change for the Reference Standard, it is proposed to change USP 5-Nitro-2-furfuraldazine RS to USP Nitrofurazone Related Compound A RS. The limit test, which has been editorially restyled, is also affected by this revision.

(PA7b: B. Davani) RTS—40397-1

Change to read:

USP Reference standards ⟨11⟩—*USP Nitrofurazone RS.* ~~*USP 5-Nitro-2-furfuraldazine RS*~~

■*USP Nitrofurazone Related Compound A RS.*■2S (*USP27*)

Change to read:

Limit of 5-nitro-2-furfuraldazine—

Adsorbent: 0.5-mm layer of chromatographic silica gel.

Test solution—Transfer 2.0 g to a 100-mL volumetric flask. Dissolve in 60 mL of dimethylformamide, dilute with acetone to volume, and mix.

Standard solution—Transfer 50.0 mg of ~~USP 5-Nitro-2-furfuraldazine RS~~

■USP Nitrofurazone Related Compound A RS■2S (*USP27*) to a 100-mL volumetric flask, dissolve in and dilute with dimethylformamide to volume, and mix.

■[NOTE—USP Nitrofurazone Related Compound A RS is 5-nitro-2-furfuraldazine.]■2S (*USP27*) Transfer 5.0 mL of this solution to a 25-mL volumetric flask, add 10 mL of dimethylformamide, dilute with acetone to volume, and mix.

Application volume: 5 µL.

Developing solvent system: a mixture of ethyl acetate and cyclohexane (4:1)

Procedure—Proceed as directed for *Thin-Layer Chromatograpy* under *Chromatography* ⟨621⟩. With a suitable densitometer, equipped with a filter having its maximum transmittance at about 254 nm, locate and scan the spot produced by the *Standard solution* and any spot from the *Test solution* having the same R_F as that produced by the *Standard solution:* the area and intensity of any spot from the *Test solution* are not greater than the area and intensity produced by the spot from the *Standard solution* (0.5%).

BRIEFING

Norgestimate, *USP 26* page 1335 and page 423 of *PF* 29(2) [Mar.–Apr. 2003]. It is proposed to revise the *Procedure* in the test for *Limit of residual solvents* to incorporate the ICH Q3C limits.

(PA1: C. Anthony) RTS—40130-1; 40096-1

Change to read:

Specific rotation ⟨781S⟩: between +40° and +46°.

Test solution: 10 mg per mL, in chloroform. ~~[NOTE—Use within 10 minutes of preparation.]~~

▲ ▲*USP27*

Change to read:

Limit of residual solvents—

Internal standard solution—Prepare a solution of isobutyl alcohol in dimethylformamide containing 2 µL of isobutyl alcohol per 100 mL of solution.

Standard solution—Prepare a solution in *Internal standard solution* containing 5 µL each of acetone, alcohol, chloroform, diisopropyl ether, and methanol per 100 mL of solution.

System suitability solution—Dilute a portion of the *Standard solution* with *Internal standard solution* to obtain a solution containing 0.05 µL each of acetone, alcohol, chloroform, diisopropyl ether, and methanol per 100 mL of solution.

Test solution—Transfer about 40 mg of Norgestimate and 2 mL of *Internal standard solution* to a 5-mL volumetric flask or a suitable vial, and shake well to dissolve.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused-silica capillary column bonded with a 1-µm layer of phase G16, and a split injection system. The detector temperature is about 250°, and the injection port temperature is about 180°. The column temperature is programmed as follows. It is maintained at about 65° for 2.5 minutes, increased at a rate of 35° per minute to 100°, maintained for 2 minutes, then at a rate of 30° per minute increased to 160°, and maintained for 2.5 minutes. The carrier gas is helium, flowing at a rate of about 6 mL per minute, and the split flow rate is about 16 mL per minute. Chromatograph the *Internal standard solution,* the *Standard solution,* and the *System suitability solution,* and record the peak responses as directed for *Procedure:* there are no interfering peaks due to dimethylformamide; the retention time of isobutyl alcohol in the chromatogram of the *Internal standard solution* is between 4 and 5 minutes; the signal-to-noise ratio for alcohol obtained from the *System suitability solution* is not less than 2.0; and the relative standard deviation for replicate injections of the *Standard solution,* determined from the peak response ratios of each solvent to the internal standard, is not more than 3.0%.

Procedure—Separately inject equal volumes (about 1 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each solvent in the portion of Norgestimate taken by the formula:

$$200(CD/W)(R_U/R_S),$$

in which C is the concentration, in mL per mL, of each solvent in the *Standard solution; D* is the density, in mg per mL, of each solvent; W is the weight, in mg, of Norgestimate taken to prepare the *Test solution;* and R_U and R_S are the peak response ratios of the appropriate analyte to the internal standard obtained from the *Test solution* and the *Standard solution*, respectively. Not more than 0.05% each of ~~acetone and diisopropyl ether is found; not more than 0.08% of alcohol is found; not more than 0.1% of chloroform is found; and not more than 0.2% of methanol is found.~~

■acetone, diisopropyl ether, and alcohol is found; not more than 0.006% of chloroform is found; and not more than 0.3% of methanol is found.■2S (*USP27*)

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Change to read:

Chromatographic purity—

TEST 1—

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

Standard solution—Use the *Standard preparation*, prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation*, prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Norgestimate taken by the formula:

$$5000(CP/W)(r_i/Fr_S),$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard solution; P* is the fraction of (*E*)-norgestimate in USP Norgestimate RS; *W* is the weight, in mg, of Norgestimate taken to prepare the *Test solution;* r_i is the peak area for each impurity obtained from the *Test solution; F* is the relative response factor and it is equal to 0.83 for any peak having a relative retention time of 0.50, 1.13 for any peak having a relative retention time of 0.56, 0.85 for any peak having a relative retention time of 0.72, and 1.0 for any other peak; and r_S is the peak area of (*E*)-norgestimate obtained from the *Standard solution.* Not more than 0.3% of total impurities having relative retention times of 0.50 and 0.56 is found; not more than 0.3% of the impurity having a relative retention time of 0.72 is found; and not more than 0.1% of any other impurity is found.

TEST 2—

Mobile phase—Prepare a filtered and degassed mixture of cyclohexane and

▲absolute▲*USP27*
alcohol (50:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Norgestimate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 1.0 mg per mL.

System suitability solution—Dilute a portion of *Standard solution* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.5 µg per mL.

Test solution—Transfer about 10 mg of Norgestimate, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 4.6-mm × 25-cm column that contains a 5-µm packing L20. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for (*E*)-norgestimate is not less than 3.0. Chromatograph the *Standard solution,* and record the peak areas as directed for *Procedure:* the retention time is about 18.6 minutes for (*E*)-norgestimate; the relative retention times are about 1.0 for (*E*)-norgestimate and 1.1 for (*Z*)-norgestimate; the tailing factor is not more than 1.5; the resolution, *R,* between (*Z*)-norgestimate and (*E*)-norgestimate is not less than 1.5; and the relative standard deviation for replicate injections, determined from the peak area of (*Z*)-norgestimate to (*E*)-norgestimate, is not more than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the percentage of each impurity in the portion of Norgestimate taken by the formula:

$$1000(CP/W)(r_i/Fr_S),$$

in which C is the concentration, in mg per mL, of USP Norgestimate RS in the *Standard solution; P* is the fraction of (*E*)-norgestimate in USP Norgestimate RS; *W* is the weight, in mg, of Norgestimate taken to prepare the *Test solution;* r_i is the peak area for each impurity obtained from the *Test solution; F* is the relative response factor and it is equal to 1.4 for any peak having a relative retention time of 0.74, 1.5 for any peak having a relative retention time of 0.78, and 1.2 for any peak having a relative retention time of 0.91; and r_S is the peak area of (*E*)-norgestimate obtained from the *Standard solution.* Not more than 0.2% of the impurity having a relative retention time of 0.74 is found; and not more than 0.1% each of the impurities having relative retention times of 0.78 and 0.91. Not more than 1.0% of total impurities is found, the results for *Test 1* and *Test 2* being added.

BRIEFING

Nortriptyline Hydrochloride Oral Solution, *USP 26* page 1339—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-11

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

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Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Ofloxacin, *USP 26* page 1347. It is proposed to delete the *Chromatographic purity* test and replace it with a *Related compounds* test that has chromatographic conditions that are reported to obtain better resolution and peak shapes. In an attempt to harmonize, this proposed procedure is based on a method in the *European Pharmacopoeia.* See also the briefing under *Acyclovir.* Note that where the Ofloxacin is labeled as sterile, it must meet the requirements under *Sterility Tests* ⟨71⟩. The *Bacterial endotoxins* test is not required at this time.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40222-1; 40237-14

Change to read:

Packaging and storage—Preserve in well-closed containers, protected from light.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Ofloxacin RS.*

■*USP Ofloxacin Related Compound A RS.*■2S (*USP27*)

Delete the following:

■~~**Chromatographic purity—**~~

~~*Mobile phase*—Dissolve 27.2 g of monobasic potassium phosphate in 1000 mL of water, adjust with phosphoric acid to a pH of 2.4, and mix. Prepare a filtered and degassed mixture of this solution and acetonitrile (90:10). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*System suitability standard solution*—Dissolve an accurately weighed quantity of USP Ofloxacin RS in methanol to obtain a solution having a known concentration of about 1.0 µg per mL.~~

~~*Test solution*—Quantitatively dissolve an accurately weighed quantity of Ofloxacin in methanol to obtain a solution containing about 1.0 mg per mL.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 294 nm detector and a 4.6 mm × 10 cm column that contains packing L1. The flow rate is about 2 mL per minute. Chromatograph the *System suitability standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency, determined from the ofloxacin peak, is not less than 1400 theoretical plates when calculated by the formula:~~

$$5.545(t_R/W_{h/2})^2,$$

~~and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram for a period of time that is 2.5 times the retention time of the main ofloxacin peak, and measure the areas for all the peaks, except to disregard the solvent peak. Calculate the percentage of desfluoroofloxacin in the portion of Ofloxacin taken by the formula:~~

$$100(1.13r_u/r_t),$$

~~in which 1.13 is the response factor of desfluoroofloxacin relative to that of ofloxacin; r_u is the area for the desfluoroofloxacin peak, if present, at a retention time of about 0.56 relative to that of ofloxacin; and r_t is the total area of the peaks, except for the solvent peak: not more than 0.2% is found. Calculate the percentage of each other impurity with an area greater than that of the ofloxacin peak in the chromatogram of the *System suitability standard solution* obtained under *Chromatographic system,* by the formula:~~

$$100(r_i/r_t),$$

~~in which r_i is the peak area for an individual impurity; and r_t is the total area of the peaks in the chromatogram obtained from the *Test solution,* except for the solvent peak: not more than 0.3% of any individual impurity is found; and the sum of all impurities found is not more than 0.5%.~~■2S (*USP27*)

Add the following:

■**Related compounds—**

Mobile phase—Dissolve 4.0 g of ammonium acetate and 7.0 g of sodium perchlorate in 1300 mL of water, adjust with phosphoric acid to a pH of 2.2, and mix. Prepare a filtered and degassed mixture of this solution and 240 mL of acetonitrile. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Transfer 10.0 mg of USP Ofloxacin Related Compound A RS and 10.0 mg of USP Ofloxacin RS to a 100-mL volumetric flask, dissolve in and dilute with a mixture of acetonitrile and water (1:6) to volume, and mix. Dilute 10.0 mL of this solution to 50.0 mL

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with a mixture of acetonitrile and water (1:6). Dilute 1.0 mL of this solution to 50.0 mL with a mixture of acetonitrile and water (1:6).

Standard solution—Quantitatively dissolve an accurately weighed quantity of USP Ofloxacin RS in a mixture of acetonitrile and water (1:6) to obtain a solution that contains 0.0004 mg per mL ofloxacin.

Test solution—Quantitatively dissolve an accurately weighed quantity of Ofloxacin in a mixture of acetonitrile and water (1:6) to obtain a solution containing about 0.2 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 294-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 0.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution between ofloxacin and ofloxacin related compound A is not less than 2.0; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Inject equal volumes (about 10 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatogram for a period of time that is about 2.5 times the retention time of the ofloxacin peak, and measure the areas for all peaks, except the solvent peak. Calculate the percentage of each impurity with an area greater than 0.1 times the average area of the ofloxacin peak obtained from the *Standard solution* by the formula:

$$100(C/C_T)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Ofloxacin RS in the *Standard solution;* C_T is the concentration, in mg per mL, of the *Test solution;* r_i is the peak area for an individual impurity; and r_S is the average area of the ofloxacin peak obtained from the *Standard solution:* not more than 0.3% of any individual impurity is found; and the sum of all impurities found is not more than 0.5%.■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Ofloxacin is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Ondansetron Hydrochloride, *USP 26* page 1351 and page 1548 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-29

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Ondansetron Hydrochloride RS. USP Ondansetron Related Compound A RS. ~~*USP Ondansetron Related Compound B RS.*~~

■*USP Ondansetron Resolution Mixture RS.*■2S (*USP27*)
USP Ondansetron Related Compound C RS. USP Ondansetron Related Compound D RS.

Change to read:

Limit of ondansetron related compound D—

Mobile phase—Prepare a filtered and degassed mixture of 0.02 M monobasic potassium phosphate (previously adjusted with 1 M sodium hydroxide to a pH of 5.4) and acetonitrile (80:20). Make

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adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Ondansetron Related Compound D RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.4 µg per mL.

System suitability solution—Dissolve suitable quantities of USP Ondansetron Related Compound D RS and USP Ondansetron Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a concentration of about 0.6 µg per mL and 1 µg per mL, respectively.

Test solution—Transfer about 50 mg of Ondansetron Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 328-nm detector and a 4.6-mm × 20-cm column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for ondansetron related compound C and 1.0 for ondansetron related compound D; and the resolution, *R,* between ondansetron related compound C and ondansetron related compound D is not less than 1.5. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency determined from the analyte peak is not less than 400 theoretical plates; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of ondansetron related compound D in the portion of Ondansetron Hydrochloride taken by the formula:

$$10(C/W)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of USP Ondansetron Related Compound D RS in the *Standard solution; W* is the weight, in mg, of Ondansetron Hydrochloride taken to prepare the *Test solution;* and r_U and r_S are the peak ~~responses~~

■areas■2S (*USP27*)
obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.10% is found.

Change to read:

Chromatographic purity—

METHOD I—

Resolution solution—Dissolve ~~an accurately weighed quantity of USP Ondansetron Related Compound A RS~~

■a quantity of USP Ondansetron Resolution Mixture RS■2S (*USP27*)
in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of ~~100 µg per mL.~~

■12.5 mg per mL.■2S (*USP27*)

~~*Identification solution*—Dissolve an accurately weighed quantity of USP Ondansetron Related Compound B RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a known concentration of 100 µg per mL.~~

■■2S (*USP27*)
Standard solutions—Dissolve an accurately weighed quantity of USP Ondansetron Hydrochloride RS in methanol, and mix to obtain a solution having a known concentration of about 0.25 mg per mL. Dilute this solution quantitatively with methanol to obtain *Standard solutions,* designated below by letter, having the following compositions:

Standard solution	Dilution	Concentration (µg RS per mL)	Percentage (%, for comparison with test specimen)
A	(1 in 5)	50	0.4
B	(1 in 10)	25	0.2
C	(1 in 20)	12.5	0.1

Test solution—Dissolve an accurately weighed quantity of Ondansetron Hydrochloride in methanol to obtain a solution containing 12.5 mg per mL.

Procedure—Separately apply 20 µL of the *Test solution,* 20 µL of each *Standard solution,* and ~~10 µL of the *Identification solution*~~

■20 µL of the *Resolution solution*■2S (*USP27*)
to a thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.25-mm layer of chromatographic silica gel mixture. ~~To the same plate apply 20 µL of the *Test solution* and on top of this application apply 10 µL of the *Resolution solution* and 10 µL of the *Identification solution* to make a system suitability spot.~~

■■2S (*USP27*)
Develop the chromatogram in a solvent system consisting of a mixture of chloroform, ethyl acetate, methanol, and ammonium hydroxide (90:50:40:1) until the solvent front has moved about three-fourths of the length of the plate. Remove the plate from the chamber, mark the solvent front, and allow the solvent to evaporate. ~~Examine the plate under short-wavelength UV light, and compare the intensities of any secondary spots observed in the chromatogram of the *Test solution* with those of the principal spots in the chromatograms of the *Standard solutions:* complete resolution of the three components of the system suitability spot, any secondary spot from the chromatogram of the *Test solution* having an R_x value corresponding to that of the principal spot of the *Identification solution* is not larger or more intense than the principal spot obtained from the *Standard solution A* (0.4%), and no other secondary spot from the chromatogram of the *Test solution*~~

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~~having an R_F value corresponding to that of the principal spot of the *Resolution solution* is larger or more intense than the principal spot obtained from *Standard solution B* (0.2%), and the sum of the intensities of the secondary spots obtained from the *Test solution* corresponds to not more than 1.0%.~~

■Examine the plate under short-wavelength UV light: complete resolution of the three components of the *Resolution solution* spot is found. Compare the intensities of any secondary spots observed in the chromatogram of the *Test solution* with those of the principal spots in the chromatograms of the *Standard solutions:* any secondary spot from the chromatogram of the *Test solution* having an R_F value corresponding to that of the uppermost secondary spot of the *Resolution solution* is not larger or more intense than the principal spot obtained from *Standard solution A* (0.4%); and no other secondary spot from the chromatogram of the *Test solution* is larger or more intense than the principal spot obtained from *Standard solution B* (0.2%).■2S (*USP27*)

METHOD II—

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

Standard solution—Proceed as directed for the *Standard preparation* in the *Assay.*

Test solution—Use the *Assay preparation*.

Procedure— ~~Inject a volume (about 10 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Ondansetron Hydrochloride taken by the formula:~~

~~$100(r_i/r_S)$,~~

~~in which r_i is the peak response for each impurity, and r_S is the sum of the responses of all of the peaks: not more than 0.2% of any individual impurity is found, and the total of all impurities found is not more than 0.5%.~~

■Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of each impurity in the portion of Ondansetron Hydrochloride taken by the formula:

$$50{,}000(C/W)(1/F)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Ondansetron Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Ondansetron Hydrochloride taken to prepare the *Test solution; F* is the relative response factor of the impurities as described in the accompanying table; r_i is the peak area for each impurity in the *Test solution;* and r_S is the peak area of ondansetron obtained from the *Standard solution:* meets the requirements given in the accompanying table.

Compound name	Relative retention time	Relative response factor	Limit (%)
Ondansetron related compound C	about 0.32	1.2	0.2
Ondansetron related compound D*	about 0.34	1.3	0.1
Imidazole	about 0.49	0.3	0.2
2-methylimidazole	about 0.54	0.4	0.2
Ondansetron	1.0	—	—
Ondansetron related compound A	about 1.10	0.8	0.2
Unknown	—	1.0	0.1
Total	—	—	0.5

* Quantified in the test for *Limit of ondansetron related compound D.*■2S (*USP27*)

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Add the following:

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

Change to read:

Assay—

Mobile phase—Prepare a filtered and degassed mixture of 0.02 M monobasic ~~potassium~~

■sodium■2S (*USP27*)
phosphate (previously adjusted with 1 M sodium hydroxide to a pH of 5.4) and acetonitrile (50:50). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Ondansetron Hydrochloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 90 µg per mL.

System suitability solution—Dissolve suitable quantities of USP Ondansetron Hydrochloride RS and USP Ondansetron Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution containing about 90 µg per mL and ~~50 µg~~

■20 µg■2S (*USP27*)
per mL, respectively.

Assay preparation—Transfer about 45 mg of Ondansetron Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 216-nm detector and a 4.6-mm × 20-cm column that contains packing L10. The flow rate is about 1.5 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.0 for ondansetron and 1.1 for ondansetron related compound A; and the resolution, *R,* between ondansetron related compound A and ondansetron is not less than 1.5. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{18}H_{19}N_3O \cdot HCl$ in the portion of Ondansetron Hydrochloride taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Ondansetron Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak ~~responses~~

■areas■2S (*USP27*)
obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Orphenadrine Citrate, *USP 26* page 1354 and page 94 of *PF* 29(1) [Jan.–Feb. 2003]—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-30

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Orphenadrine Citrate RS.

Change to read:

~~**Chromatographic purity—**~~

▲**Related compounds**—▲*USP27*

~~*Standard preparation*—Transfer 50 mg, accurately weighed, of USP Orphenadrine Citrate RS to a 10-mL volumetric flask, add about 7 mL of methanol, and swirl to dissolve. Dilute with methanol to volume, and mix.~~

~~*Test preparation*—Prepare as directed under *Standard preparation,* using Orphenadrine Citrate instead of the Reference Standard.~~

~~*Procedure*—Divide a thin-layer chromatographic plate, coated with chromatographic silica gel mixture, into two equal parts. Apply 20 µL of *Standard preparation* in 5-µL portions to one part of the plate, drying after each application, and similarly apply 20 µL of *Test preparation* to the second part of the plate. Allow the spots to dry, and develop the chromatogram in an unsaturated chamber in a solvent system consisting of a mixture of methanol and ammonium hydroxide (100 : 1) until the solvent front has moved at least 10 cm from the origin. Remove the plate from the chamber, and allow the solvent to evaporate. Irradiate the plate under short-wavelength UV light, and without delay locate the spots by visual inspection: the R_f value of the principal spot obtained from the *Test*~~

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~~*preparation* corresponds to that obtained from the *Standard preparation,* and no spots are observed other than the principal spot and a spot at the origin representing residual citrate.~~

▲*0.05 M Ammonium phosphate buffer, Mobile phase, System sensitivity solution,* and *Chromatographic system*—Prepare as directed in the *Assay.*

Standard solution—Use the *Standard preparation,* prepared as directed in the *Assay.*

Test solution—Use the *Assay preparation,* prepared as directed in the *Assay.*

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution* and the *Standard solution* into the chromatograph, record the chromatogram for at least 2.5 times the retention time of orphenadrine citrate, and measure all of the peak areas. Calculate the percentage of each impurity in the portion of Orphenadrine Citrate taken by the formula:

$$5000F(C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Orphenadrine Citrate RS in the *Standard solution; W* is the weight, in mg, of Orphenadrine Citrate taken to prepare the *Test solution; F* is the relative response factor and is equal to 0.75 for any peak at a relative retention time of about 0.25, 0.41 for any peak at a relative retention time of about 0.51, 0.52 for any peak at a relative retention time of about 1.54, and 1.0 for any other peak; r_i is the peak area for each impurity in the *Test solution;* and r_S is the peak area of orphenadrine citrate in the *Standard solution:* not more than 0.5% of total impurities is found.▲*USP27*

Add the following:

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

Change to read:

Assay— ~~Dissolve about 1 g of Orphenadrine Citrate, accurately weighed, in 50 mL of glacial acetic acid, add 1 drop of crystal violet TS, and titrate with 0.1 N perchloric acid VS to a blue endpoint. Perform a blank determination, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 46.15 mg of $C_{18}H_{23}NO \cdot C_6H_8O_7$.~~

▲*0.05 M Ammonium phosphate buffer*—Dissolve 5.8 g of monobasic ammonium phosphate in 1000 mL of water, and adjust with ammonium hydroxide or phosphoric acid to a pH of 7.9 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of methanol, *0.05 M Ammonium phosphate buffer,* and acetonitrile (9:8:3). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Orphenadrine Citrate RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.9 mg per mL.

System sensitivity solution—Dilute a volume of *Standard preparation* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.00045 mg per mL

Assay preparation—Transfer about 45 mg of Orphenadrine Citrate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 15-cm column that contains 5-µm packing L1. The flow rate is about 1.5 mL per minute. The column temperature is maintained at 40°. Chromatograph the *Standard preparation,* and record the peak areas as directed for *Procedure:* the column efficiency is not less

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than 4500 theoretical plates; the tailing factor is not more than 2.0; and the relative standard deviation for replicate injections is not more than 2.0%. Chromatograph the *System sensitivity solution,* and record the peak areas as directed for *Procedure:* the signal-to-noise ratio is not less than 10.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the area for the orphenadrine citrate peaks. Calculate the quantity, in mg, of $C_{18}H_{23}NO \cdot C_6H_8O_7$ in the portion of Orphenadrine Citrate taken by the formula:

$$50C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Orphenadrine Citrate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.▲*USP27*

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Oxymorphone RS.

Add the following:

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

BRIEFING

Oxymorphone Hydrochloride, *USP 26* page 1376—See briefing under *Alfentanil Hydrochloride*.

(PA2: C. Anthony; PSD: C. Okeke) RTS—40355-1

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Oxytocin, *USP 26* page 1385—See briefing under *Acepromazine Maleate*.

(BNT: I. DeVeau) RTS—40270-15

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Oxytocin RS. USP Vasopressin RS.

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Add the following:

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

BRIEFING

Paclitaxel, *USP 26* page 1386 and page 3107 of the *Second Supplement.* In the *Packaging and storage* section, it is proposed to replace "store between 20° and 25°" with "store at controlled room temperature". It is also proposed to increase the combined limit of cephalomannine and 2″,3″-dihydrocephalomannine in *Table 1* of the test for *Related compounds* from not more than 0.5% to not more than 0.8%.

(PA6: L. Evans) RTS—39780-1; 39513-3

Change to read:

Packaging and storage—Preserve in tight, light-resistant containers, ■and store ~~between 20° and 25°.~~■2S (*USP26*)

■at controlled room temperature.■2S (*USP27*)

Change to read:

Related compounds—

TEST 1 *(for material labeled as isolated from natural sources)*—If the material complies with this test, the labeling indicates that it meets *USP Related compounds Test 1.*

Diluent—Prepare as directed in the *Assay.*

Solution A—Prepare filtered and degassed acetonitrile.

Solution B—Prepare filtered and degassed water.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Paclitaxel Related Compound A RS and USP Paclitaxel Related Compound B RS in methanol to obtain a solution having known concentrations of about 10 µg of each per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix.

Standard solution—Dissolve, with the aid of sonication, an accurately weighed quantity of USP Paclitaxel RS in *Diluent,* and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 5 µg per mL.

Test solution—Use the *Assay preparation.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L43. The flow rate is about 2.6 mL per minute. The column temperature is maintained at 30°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–35	35	65	isocratic
35–60	35→80	65→20	linear gradient
60–70	80→35	20→65	linear gradient
70–80	35	65	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.78 for paclitaxel related compound A and 0.86 for paclitaxel related compound B (relative to the retention time for paclitaxel obtained from the *Test solution*); and the resolution, *R,* between paclitaxel related compound A and paclitaxel related compound B is not less than 1.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Inject a volume (about 15 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$100(Fr_i / r_U),$$

in which F is the relative response factor for each impurity peak (see *Table 1* for values); r_i is the peak area for each individual impurity; and r_U is the peak area for paclitaxel.

Table 1

Relative Retention Time	Relative Response Factor *(F)*	Name	Limit (%)
0.24	1.29	Baccatin III	0.2
0.53	1.00	10-Deacetylpaclitaxel	0.5
0.57	1.00	7-Xylosylpaclitaxel	0.2
0.78	1.26	Cephalomannine (paclitaxel related compound A)	a_1[1]
0.78	1.26	2″,3″-Dihydrocephalomannine	a_2[1]
0.86	1.00	10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B)	0.5
1.10	1.00	Benzyl analog[3]	b_1[2]
1.10	1.00	3″,4″-Dehydropaclitaxel C	b_2[2]
1.40	1.00	7-Epicephalomannine	0.3
1.85	1.00	7-Epipaclitaxel	0.5

[1] Resolution may be incomplete for these peaks depending upon the relative amounts present; the sum of a_1 and a_2 is not more than ~~0.5%.~~

■0.8%.■2S (*USP27*)

[2] Resolution may be incomplete for these peaks depending upon the relative amounts present; the sum of b_1 and b_2 is not more than 0.5%.

[3] The following chemical name is assigned to the related compound, benzyl analog: Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(2-phenylacetylamino)propanoic acid.

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In addition to not exceeding the limits for paclitaxel related impurities in *Table 1*, not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities is found.

TEST 2 *(for material labeled as produced by a semisynthetic process)*—If the material complies with this test, the labeling indicates that it meets *USP Related compounds Test 2.*

Diluent—Use acetonitrile.

Solution A—Use a filtered and degassed mixture of water and acetonitrile (3:2).

Solution B—Use filtered and degassed acetonitrile.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Paclitaxel RS and USP Paclitaxel Related Compound B RS in *Diluent,* using shaking and sonication if necessary, to obtain a solution having known concentrations of about 0.96 mg per mL and 0.008 mg per mL, respectively.

Test solution—Transfer about 10 mg of Paclitaxel, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, using shaking and sonication if necessary, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 227-nm detector and a 4.6-mm × 15-cm column that contains 3-µm packing L1. The flow rate is about 1.2 mL per minute. The column temperature is maintained at 35°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–20	100	0	isocratic
20–60	100→10	0→90	linear gradient
60–62	10→100	90→0	linear gradient
62–70	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.94 for paclitaxel related compound B and 1.0 for paclitaxel; the resolution, *R,* between paclitaxel related compound B and paclitaxel is not less than 1.2; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 15 µL) of the *Diluent* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all of the peaks. Disregard any peaks due to the *Diluent.* Calculate the percentage of each impurity in the portion of Paclitaxel taken by the formula:

$$100(Fr_i / r_s),$$

in which F is the relative response factor for each impurity (see *Table 2* for values); r_i is the peak area for each impurity obtained from the *Test solution;* and r_s is the sum of the areas of all the peaks obtained from the *Test solution.* In addition to not exceeding the limits for paclitaxel related impurities in *Table 2,* not more than 0.1% of any other single impurity is found; and not more than 2.0% of total impurities is found.

Table 2

Relative Retention Time	Relative Response factor (*F*)	Name	Limit (%)
0.11	1.24	10-Deacetylbaccatin III	0.1
0.20	1.29	Baccatin III	■0.2■2S (*USP26*)
0.42	1.39	Photodegradant[2]	0.1
0.47	1.00	10-Deacetylpaclitaxel	0.5
0.80	1.00	2-Debenzoylpaclitaxel-2-pentenoate	0.7
0.92[1]	1.00	Oxetane ring opened, acetyl and benzoyl[2]	x_1
0.92[1]	1.00	10-Acetoacetylpaclitaxel	x_2
0.94[1]	1.00	10-Deacetyl-7-epipaclitaxel (paclitaxel related compound B)	x_3
1.37	1.00	7-Epipaclitaxel	0.4
1.45	1.00	10,13-Bissidechainpaclitaxel[2]	0.5
1.54	1.00	7-Acetylpaclitaxel	0.6
1.80	1.75	13-Tes-baccatin III	0.1
2.14	1.00	7-Tes-paclitaxel	0.3

[1] Resolution may be incomplete for these peaks depending upon the relative amounts present; the sum of x_1, x_2, and x_3 is not more than 0.4%.

[2] The following chemical names are assigned to the related compounds Photodegradant, Oxetane ring opened, acetyl and benzoyl, and 10,13-Bissidechainpaclitaxel:

Photodegradant
(1*R*,2*R*,4*S*,5*S*,7*R*,10*S*,11*R*,12*S*,13*S*,15*S*,16*S*)-2,10-diacetyloxy-5,13-dihydroxy-4,16,17,17-tetramethyl-8-oxa-3-oxo-12-phenylcarbonyloxypentacyclo[11.3.1.$0^{1,11}$.$0^{4,11}$.$0^{7,10}$]heptadec-15-yl(2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoate

Oxetane ring opened, acetyl and benzoyl(1*S*,2*S*,3*R*,4*S*,5*S*,7*S*,8*S*,10*R*,13*S*)-5,10-diacetyloxy-1,2,4,7-tetrahydroxy-8,12,15,15-tetramethyl-9-oxo-4-(phenylcarbonyloxymethyl)tricyclo[9.3.1.$0^{3,8}$]pentadec-11-en-13-yl(2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoate

10,13-Bisside-chainpaclitaxel Baccatin III 13-ester with (2*R*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoic acid, 10-ester with (2*S*,3*S*)-2-hydroxy-3-phenyl-3-(phenylcarbonylamino)propanoic acid

BRIEFING

Paroxetine Hydrochloride, page 100 of *PF* 29(1) [Jan.–Feb. 2003]. It is proposed to revise the *Packaging and storage* section to add the storage temperature. It is also proposed not to include the melting range test for this product. One of the limits for the impurities in the *Procedure* under *Chromatographic purity Test 1* is proposed to be modified because two possible impurities elute at the relative retention time of paroxetine related compound B. Other minor editorial revisions have also been made.

(PA3: S. Salado) RTS—39464-1; 39620-1; 39480-1

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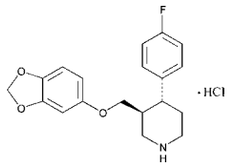
Add the following:

■Paroxetine Hydrochloride



$C_{19}H_{20}FNO_3 \cdot HCl$ 365.83

Piperidine, 3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-, hydrochloride, (3*S*-*trans*)-.

(–)-(3*S*,4*R*)-4-(*p*-Fluorophenyl)-3-[(3,4-methylenedioxy)-phenoxy]methyl]piperidine hydrochloride [*78246-49-8*].

Hemihydrate 374.83 ~~[*CAS to come*].~~

» Paroxetine Hydrochloride is anhydrous or contains one-half molecule of water of hydration. It contains not less than 98.5 percent and not more than 102.0 percent of $C_{19}H_{20}FNO_3 \cdot HCl$, calculated on the anhydrous and solvent-free basis.

Packaging and storage—Preserve the anhydrous form in tight containers. Preserve the hemihydrate form in well-closed containers. Store between 15° and 30°.

Labeling—Label it to indicate whether it is the anhydrous or the hemihydrate form. Label it to indicate with which impurity tests the article complies.

USP Reference standards ⟨11⟩—*USP Paroxetine Hydrochloride RS. USP Paroxetine Related Compound A RS. USP Paroxetine Related Compound B RS. USP Paroxetine Related Compound C RS.* ~~*USP Paroxetine Related Compound D RS.*~~ *USP Paroxetine Related Compound E RS. USP Paroxetine Related Compound F RS. USP Paroxetine Related Compound G RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩—

Test specimen—Dissolve a suitable portion of Paroxetine Hydrochloride in a solution of water in isopropyl alcohol (1 in 10), heat to 70° to dissolve, recrystallize, ~~and use the residue.~~ and dry the residue under vacuum at 50° for 3 hours.

Standard specimen: a similar preparation of USP Paroxetine Hydrochloride RS.

B: A solution (1 in 100) in a mixture of methanol and water (1:1) meets the requirements of the test for *Chloride* ⟨191⟩.

~~**Melting range,** *Class I* ⟨741⟩: between 115° and 126° for the anhydrous form; [To come for the anhydrous form] between 141° and 145° for the hemihydrate form.~~

Water, *Method I* ⟨921⟩: not more than ~~1.5%~~ 1.0% for the anhydrous form and between ~~2.0%~~ 2.2% and ~~3.0%~~ 2.8% for the hemihydrate form.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.002%.

~~**Limit of stereoisomers**~~ **Limit of related compound C**—

~~*Mobile phase*—Prepare a filtered and degassed mixture of 0.5 M sodium chloride and methanol (4:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

~~*0.05 M Phosphate buffer solution*—Dissolve 8.7 g of dibasic potassium phosphate in 1000 mL of water, and adjust with phosphoric acid to a pH of 6.5.~~

~~*Mobile phase*—Prepare a filtered and degassed mixture of *0.05 M Phosphate buffer solution* and acetonitrile (92:8). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).~~

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System suitability solution—Transfer about 5 mg of USP Paroxetine Hydrochloride Related Compound C RS and about 5 mg of USP Paroxetine Hydrochloride RS, accurately weighed, to a 10 mL volumetric flask. Dissolve in 1 mL of methanol, dilute with *Mobile phase* to volume, and mix.

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Related Compound C RS and USP Paroxetine Hydrochloride RS in methanol, the volume of the solvent not exceeding 20% of the final solution volume, and dilute quantitatively with 0.5 M sodium chloride to obtain a solution having a known concentration of about 0.01 mg of each USP Reference Standard per mL. If stepwise dilution is necessary, dilute with *Mobile phase* instead.

Test solution—Transfer about 100 mg of Paroxetine Hydrochloride, accurately weighed, to a 100 mL volumetric flask, dissolve in 20 mL of methanol, dilute with 0.5 M sodium chloride to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 295 nm detector and a 4 mm × 10 cm column that contains packing L41. The flow rate is about 0.5 mL per minute. Chromatograph the *Standard System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.56 for paroxetine related compound C and 1.0 for paroxetine; the resolution, *R,* between paroxetine related compound C and paroxetine is not less than 1.8; the column efficiency determined from the related compound C peak is not less than 230 theoretical plates; the tailing factor for the paroxetine related compound C peak is not more than 1.6; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes Inject a volume (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses. Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride taken by the formula:

$$10(C/W)(r_C/r_S),$$

or

$$100(r_C/r_T),$$

in which C is the concentration, in µg per mL, of USP Paroxetine Related Compound C RS in the *Standard solution;* W is the quantity, in mg, of Paroxetine Hydrochloride in the *Test solution;* and r_C and r_S are the peak responses for paroxetine related compound C obtained from the *Test solution* and the *Standard solution,* respectively; in which r_C is the peak response for paroxetine related compound C, and r_T is the sum of the responses of all of the peaks: not more than 0.1% is found.

LIMIT OF RELATED COMPOUND D—

Phosphate buffer—Prepare a 0.05 M monobasic sodium phosphate solution in water, adjust with phosphoric acid to a pH of 3.0, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (3:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve accurately weighed quantities of USP Paroxetine Related Compound D RS and USP Paroxetine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having known concentrations of about 0.1 and 1.0 mg per mL, respectively.

Test solution—Transfer about 100 mg of Paroxetine Hydrochloride, accurately weighed, to a 50 mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 295 nm detector and a 4.6 mm × 25 cm column that contains packing

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~~L13. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.2 for paroxetine related compound D and 1.0 for paroxetine; the resolution, *R,* between paroxetine related compound D and paroxetine is not less than 2.2; the column efficiency determined from the paroxetine related compound D peak is not less than 4000 theoretical plates; the tailing factor for the related compound D peak is not more than 1.8; and the relative standard deviation for replicate injections is not more than 2.5%.~~

~~*Procedure*—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound D in the portion of Paroxetine Hydrochloride taken by the formula:~~

~~$5(C/W)(r_u/r_s)$,~~

~~in which *C* is the concentration, in µg per mL, of USP Paroxetine Related Compound D RS in the *Standard solution; W* is the quantity, in mg, of Paroxetine Hydrochloride in the *Test solution;* and r_u and r_s are the peak responses for paroxetine related compound D obtained from the *Test solution* and the *Standard solution,* respectively: the sum of the percentages found in the *Limit of related compound C* and the *Limit of related compound D* tests is not more than 0.1%.~~

Mobile phase—Prepare a mixture of *n*-hexane, alcohol, water, and trifluoroacetic acid (900:100:2:2). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: a mixture of alcohol and *n*-hexane (1:1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Related Compound C RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1 mg per mL.

Test solution—Transfer about 125 mg of Paroxetine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

System suitability solution—Dilute known volumes of the *Test solution* and the *Standard solution* with *Diluent* to obtain a solution having known concentrations of about 0.1 mg per mL of each of ~~USP~~ Paroxetine Hydrochloride ~~RS~~ and of USP Paroxetine Related Compound C RS.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 295-nm detector and a 4.6-mm × 25-cm column that contains packing ~~L49.~~ L51. The flow rate is about 1.0 mL per minute, and the column temperature is maintained at 30°. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times for paroxetine and paroxetine related compound C is 1.0 and about 0.6, respectively; the resolution, *R,* between paroxetine and paroxetine related compound C is not less than 2.0; and the tailing factor for paroxetine related compound C is not greater than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0% for the paroxetine related compound C.

Procedure—Separately inject equal volumes (about 5 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the re-

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sponses for the major peaks. Calculate the percentage of paroxetine related compound C in the portion of Paroxetine Hydrochloride taken by the formula:

~~$10{,}000(C/W)(r_i/r_s)$,~~

$$2500(C/W)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Paroxetine Related Compound C RS in the *Standard solution;* W is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* and r_i and r_S are the peak areas for paroxetine related compound C in the *Test solution* and the *Standard solution,* respectively: not more than of 0.1% of paroxetine related compound C is found.

Limit of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine—

Solution A—Prepare a filtered and degassed mixture of acetonitrile and trifluoroacetic acid (1000:1).

Solution B—Prepare a filtered and degassed mixture of water and trifluoroacetic acid (1000:1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Related Compound E RS in a mixture of *Solution B* and *Solution A* (7:3), and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine of about ~~0.2~~ 100 ng per mL.

Test solution—Transfer about 20 mg of Paroxetine Hydrochloride, accurately weighed, to a suitable flask, add 1.0 mL of a mixture of *Solution B* and *Solution A* (7:3), and shake to dissolve.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a tandem mass spectrophotometric detector, monitoring the mass-to-charge ratio of 44 arising from the fragmentation of mass-to-charge ratio of 192, and a 2.0-mm × 25-cm column that contains base-deactivated packing L1. The flow rate is about 0.15 mL per minute. The collision-induced disassociation sector is filled with sufficient argon gas to produce –20 eV collisions. Adjust the argon gas pressure as necessary. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	30	70	equilibration
0–10	30	70	isocratic
10–10.5	30→90	70→10	linear gradient
10.5–20	90	10	isocratic
20–20.5	90→30	10→70	linear gradient
20.5–30	30	70	isocratic

Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio for the analyte response at a mass-to-charge ratio of 44 is not less than 5; and the relative standard deviation for replicate injections is not more than 5.0%. [NOTE—A large peak due to paroxetine is observed at about 10 minutes in this system. Divert the flow of eluate from the mass spectrometer at about 10 minutes after injection.]

Procedure—Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the

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responses for the major peaks. Calculate the amount, in ~~pg~~ ng, of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in the portion of Paroxetine Hydrochloride taken by the formula:

$$CI(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Paroxetine Related Compound E RS in the *Standard solution; I* is the amount, in ng, ~~per g,~~ of 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine in each mg of USP Paroxetine Related Compound E RS in the *Standard solution;* and r_U and r_S are the peak responses for 1-methyl-4-(*p*-fluorophenyl)-1,2,3,6-tetrahydropyridine obtained from the *Test solution* and the *Standard solution,* respectively: not more than ~~200 pg 100 ng~~ 20 ng is found (0.0001%).

Chromatographic purity—[NOTE—Perform ~~both~~ all related impurities methods unless the manufacturer has assurance, based on knowledge of the manufacturing process, that one of the tests is not relevant to their material.]

TEST 1—

Solution A—Prepare a filtered and degassed mixture of water, tetrahydrofuran, and trifluoroacetic acid (180:20:1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, tetrahydrofuran, and trifluoroacetic acid (180:20:1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: a mixture of water and tetrahydrofuran (9:1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, and dilute quantitatively, and stepwise if necessary, with *Diluent* to obtain a solution having a known concentration of about 1 µg per mL.

System suitability solution—Dissolve, by sonication if necessary, suitable quantities of USP Paroxetine Related Compound A RS and USP Paroxetine Related Compound B RS in ~~a mixture of water and tetrahydrofuran (9:1)~~ *Diluent* to obtain a solution having known concentrations of about 0.01 mg of each USP Reference Standard per mL.

Test solution—Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a 25-mL volumetric flask, dissolve in 20 mL of ~~a mixture of water and tetrahydrofuran (9:1),~~ *Diluent,* sonicate, dilute with ~~a mixture of water and tetrahydrofuran (9:1)~~ *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 285-nm detector ~~capable of monitoring at 263 and 295 nm~~ and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is about 1 mL per minute. The column temperature is maintained at 40°. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	80	20	equilibration
0–30	80	20	isocratic
30–50	80→20	20→80	linear gradient
50–60	20	80	isocratic
60–70	20→80	80→20	linear gradient

~~Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between paroxetine related compound A and paroxetine related compound B is not less than 1.5; the column efficiency determined from the paroxetine related compound A peak is not less than 10,000 theoretical plates; the tailing factor for the paroxetine related compound A peak is not more than 1.2; and the relative standard deviation for replicate injections is not more than 1.0%.~~

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~~*Procedure*—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure all of the peak responses at both 263 and 295 nm. Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken by the formula:~~

~~$100(r_i/r_s)$,~~

~~in which r_i is the peak response for each impurity; and r_s is the sum of the responses of all of the peaks: not more than 0.1% of any individual impurity is found, and not more than 0.5% of total impurities is found.~~

~~Time (minutes)~~	~~*Solution A* (%)~~	~~*Solution B* (%)~~	~~Elution~~
~~0~~	~~80~~	~~20~~	~~equilibration (for 10 minutes)~~
~~0–30~~	~~80~~	~~20~~	~~isocratic~~
~~30–50~~	~~80→20~~	~~20→80~~	~~linear gradient~~
~~50–end~~	~~20~~	~~80~~	~~isocratic~~

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 1.1 for paroxetine related compound B, and 1.0 for paroxetine related compound A; the resolution, *R,* between paroxetine related compound A and paroxetine related compound B is not less than 2.0; the tailing factor of the paroxetine related compound A peak is between 0.8 and 2.0; ~~Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:*~~ and the relative standard deviation for replicate injections is not more than 2.0% for paroxetine related compound A.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution, Test solution,* and *Diluent* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of each impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$2500(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* r_U is the peak area of each impurity in the *Test solution,* excluding the peaks obtained in the chromatogram of the *Diluent;* and r_S is the peak area of paroxetine obtained in the *Standard solution:* not more than of ~~0.5%~~ 0.3% of any peak at a retention time of paroxetine related compound B is found; not more that 0.1% of any other individual impurity is found; and not more than 1.0% of total impurities is found.

TEST 2—

Phosphate buffer—Dissolve 3.4 g of monobasic potassium phosphate and 3.4 g of tetrabutylammonium hydrogen sulfate in 1.0 liter of water.

Solution A—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (98:2).

Solution B—Prepare a filtered and degassed mixture of *Phosphate buffer* and acetonitrile (6:4).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent: a mixture of *Phosphate buffer* and acetonitrile (9:1).

Standard solution—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in *Diluent,* and dilute quantitatively, and stepwise if

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necessary, with *Diluent* to obtain a solution having known concentrations of about 4 µg per mL, 10 µg per mL, 10 µg per mL, and 4 µg per mL, respectively.

Identification solution—Dissolve an accurately weighed quantity of Paroxetine Hydrochloride, USP Paroxetine Related Compound B RS, USP Paroxetine Related Compound F RS, and USP Paroxetine Related Compound G RS in *Diluent* to obtain a solution having known concentrations of about 2 mg per mL, 10 µg per mL, 10 µg per mL, and 4 µg per mL, respectively.

Test solution—Transfer about 25 mg of Paroxetine Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Diluent* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 210-nm detector and a 3.9-mm × 15-cm column that contains packing L1. The flow rate is about 1.0 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–5	100	0	isocratic
5–70	100→40	0→60	linear gradient
70–90	40→0	60→100	linear gradient
90–95	0	100	isocratic
95–95.1	0→100	100→0	linear gradient
95.1–110	100	0	re-equilibration

Chromatograph the *Identification solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.91 for paroxetine related compound B, about 0.96 for paroxetine related compound F, 1.0 for paroxetine, and about 1.34 for paroxetine related compound G. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 10.0% for the paroxetine related compound B, paroxetine related compound F, paroxetine hydrochloride, and paroxetine related compound G peaks.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the percentage of paroxetine related compound B, paroxetine related compound F, and paroxetine related compound G in the portion of Paroxetine Hydrochloride taken by the formula:

$$5000(C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* and r_i and r_S are the peak areas for the corresponding impurity in the *Test solution* and the *Standard solution,* respectively: not more than of 0.5% of paroxetine related compound B is found; not more than 0.2% of paroxetine related compound F is found; and not more than 0.2% of paroxetine related compound G is found. Calculate the percentage of any unknown impurity in the portion of Paroxetine Hydrochloride taken by the formula:

$$5000(C/W)(r_i / r_S),$$

in which C is the concentration, in mg per mL, of the USP Paroxetine Hydrochloride RS in the *Standard solution; W* is the weight, in mg, of Paroxetine Hydrochloride, on the anhydrous basis, used to prepare the *Test solution;* r_i is the peak area for any unknown impurity in the *Test solution;* and r_S is the peak area of paroxetine in the *Standard solution:* not more than of 0.1 % of any single unknown impurity is found, and not more than 1.0% of total impurities is found.

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Organic volatile impurities, *Method V* ⟨467⟩: meets the requirements.

Assay—

Acetate buffer—Prepare a 0.05 M solution of ammonium acetate in water, adjust with glacial acetic acid to a pH of 4.5, mix, and filter.

Mobile phase—Prepare a filtered and degassed mixture of *Acetate buffer,* acetonitrile, and triethylamine (60:40:1). Adjust with glacial acetic acid to a pH of 5.5. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve suitable quantities of USP Paroxetine Related Compound B RS and USP Paroxetine Hydrochloride RS in water to obtain a solution having known concentrations of about 0.5 mg of each USP Reference Standard per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Paroxetine Hydrochloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Paroxetine Hydrochloride, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 295-nm detector and a 4.6-mm × 25-cm column that contains packing L13. The flow rate is about 1 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.9 for paroxetine related compound B and 1.0 for paroxetine; the resolution, *R,* between paroxetine related compound B and paroxetine is not less than 2.0; the column efficiency determined from the paroxetine peak is not less than 3000 theoretical plates; the tailing factor for the paroxetine peak is not more than 1.6; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{19}H_{20}FNO_3 \cdot HCl$ in the portion of Paroxetine Hydrochloride taken by the formula:

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Paroxetine Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Pentobarbital, *USP 26* page 1429 and page 655 of *PF* 29(3) [May–June 2003]—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-31

Change to read:

» Pentobarbital contains not less than ~~98.5~~ ■98.0■1S (*USP27*) percent and not more than ~~101.0~~ ■102.0■1S (*USP27*) percent of $C_{11}H_{18}N_2O_3$, calculated on the dried basis.

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

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Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Pentobarbital RS.

Change to read:

Identification—

A: *Infrared Absorption* ⟨197S⟩—
Solution: 7 in 100.
Medium: chloroform.

B: *Ultraviolet Absorption* ⟨197U⟩—
Solution: 16 µg per mL.
Medium: 0.1 N sodium hydroxide. ~~Absorptivities at 240 nm, calculated on the dried basis, do not differ by more than 3.0%.~~

■■1S (*USP27*)

C: ~~Shake about 300 mg with 5 mL of sodium hydroxide solution (1 in 125) for 2 minutes, filter, and to 1 mL of the filtrate add about 1.2 mL of silver nitrate TS: a white precipitate is formed, and it is soluble in 6 N ammonium hydroxide. To a second 1-mL portion of the filtrate add 3 drops of mercuric chloride TS: a white precipitate is formed, and it is soluble in 6 N ammonium hydroxide.~~

■The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*■1S (*USP27*)

Add the following:

■**Related compounds—**

Mobile phase—Prepare as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Pentobarbital RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.001 mg per mL.

Test solution—Transfer about 100 mg of Pentobarbital, accurately weighed, to a 100-mL volumetric flask, add about 80 mL of *Mobile phase,* and sonicate until dissolved. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 2.5; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 15.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Pentobarbital taken by the formula:

$$(10{,}000/F)(C/W)(r_i/r_S),$$

in which C is the concentration, in mg per mL, of USP Pentobarbital RS in the *Standard solution; F* is the relative response factor of the impurity according the table below; W is the weight, in mg, of pentobarbital, on dried basis, used to prepare the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for pentobarbital in the *Standard solution:* the impurities meet the requirements given in the table below:

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Compound name	Relative retention time	Relative Response Factor	Limit (%)
6-Imino-5-ethyl-5-(1-methylbutyl) barbituric acid	about 0.39	1.5	0.2
Pentobarbital	1.0	—	—
5-Ethyl-5-(1,3-dimethylbutyl) barbituric acid	about 1.5	0.9	0.3
Unknown impurities	—	1.0	0.1
Total	—	—	0.5

■1S (*USP27*)

Add the following:

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

Change to read:

Assay—

~~*0.1 N Tetrabutylammonium hydroxide in chlorobenzene*—Dilute 100 mL of 1 N tetrabutylammonium hydroxide VS with chlorobenzene to 1000 mL, and mix.~~

~~*Standardization of 0.1 N tetrabutylammonium hydroxide in chlorobenzene*—Dissolve about 180 mg, accurately weighed, of primary standard benzoic acid in about 100 mL of acetone, and titrate with *0.1 N Tetrabutylammonium hydroxide in chlorobenzene*, determining the endpoint potentiometrically, using a glass electrode and a calomel electrode containing 0.1 N methanolic tetrabutylammonium chloride (see *Titrimetry* ⟨541⟩). Each mL of *0.1 N Tetrabutylammonium hydroxide in chlorobenzene* is equivalent to 12.21 mg of benzoic acid.~~

~~*Procedure*—Transfer about 330 mg of Pentobarbital, accurately weighed, to a suitable beaker, and dissolve in 100 mL of acetone. Titrate with *0.1 N Tetrabutylammonium hydroxide in chlorobenzene*, determining the endpoint potentiometrically, using a glass electrode and a calomel electrode containing 0.1 N methanolic tetrabutylammonium chloride. Each mL of *0.1 N Tetrabutylammonium hydroxide in chlorobenzene* is equivalent to 22.63 mg of $C_{11}H_{18}N_2O_3$.~~

■*Mobile phase*—Prepare a filtered and degassed pH 3.5 mixture of 0.01 M monobasic potassium phosphate and acetonitrile (65: 35). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Pentobarbital RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.1 mg per mL.

Assay preparation—Transfer about 100 mg of Pentobarbital, accurately weighed, to a 100-mL volumetric flask, add about 80 mL of *Mobile phase,* and sonicate until dissolved. Dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the capacity factor, k', is not less than 2.5; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

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measure the peak responses for the major peak. Calculate the quantity, in mg, of $C_{11}H_{18}N_2O_3$ in the portion of Pentobarbital taken by the formula:

$$1000C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Pentobarbital RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP27*)

BRIEFING

Pentobarbital Sodium, *USP 26* page 1431 and page 1558 of *PF* 29(5) [Sept.–Oct. 2003]—See briefing under *Amitriptyline Hydrochloride*.

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-32

Change to read:

» Pentobarbital Sodium contains not less than ~~98.5~~ ■98.0■1S (*USP27*) percent and not more than ~~101.0~~ ■102.0■1S (*USP27*) percent of $C_{11}H_{17}N_2NaO_3$, calculated on the dried basis.

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Pentobarbital RS.

Change to read:

Identification—

A: ~~The UV absorption spectrum of the *Assay preparation* corresponds to that of the *Standard preparation*, as obtained in the *Assay.*~~

■*Ultraviolet Absorption* ⟨197U⟩—

Solution: 10 µg per mL.

Medium: dilute ammonium hydroxide (1 in 200).■1S (*USP27*)

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

C: ■1S (*USP27*) Ignite about 200 mg: the residue effervesces with acids, and meets the requirements of the tests for *Sodium* ⟨191⟩.

Add the following:

■**Related compounds—**

Mobile phase—Prepare as described in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Pentobarbital RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.001 mg per mL.

Test solution—Transfer about 110 mg of Pentobarbital Sodium, accurately weighed, to a 100-mL volumetric flask, add about 80 mL of *Mobile phase,* and sonicate until dissolved. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm

packing L1. The flow rate is about 1.0 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the capacity factor, *k′,* is not less than 2.5; the column efficiency is not less than 15,000 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 15.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of any impurity in the portion of Pentobarbital Sodium taken by the formula:

$$(248.25/226.27)(10{,}000/F)(C/W)(r_i/r_S),$$

in which 248.25 and 226.27 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; C is the concentration, in mg per mL, of USP Pentobarbital RS in the *Standard solution; F* is the relative response factor of the impurity according to the table below; W is the weight, in mg, of Pentobarbital Sodium, on the dried basis, used to prepare the *Test solution;* r_i is the peak area for any impurity in the *Test solution;* and r_S is the peak area for Pentobarbital in the *Standard solution:* the impurities meet the requirements given in the table below:

Compound Name	Relative Retention Time	Relative Response Factor	Limit (%)
6-Imino-5-ethyl-5-(1-methylbutyl)barbituric acid	about 0.39	1.5	0.2
Pentobarbital	1.0	—	—
5-Ethyl-5-(1,3-dimethylbutyl) barbituric acid	about 1.5	0.9	0.3
Unknown impurities	—	1.0	0.1
Total	—	—	0.5

■1S (*USP27*)

Add the following:

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

Change to read:

Assay—

~~*Diluting solvent*—Use freshly prepared dilute ammonium hydroxide (1 in 200).~~

~~*Standard preparation*—Dissolve an accurately weighed quantity of USP Pentobarbital RS in *Diluting solvent* to obtain a solution having a known concentration of about 10 µg per mL.~~

~~*Assay preparation*—Transfer about 25 mg of pentobarbital sodium, previously dried and accurately weighed, in a 50-mL volumetric flask, immediately dilute with *Diluting solvent* to volume, and mix. Pipet 2 mL of this solution into a 100-mL volumetric flask, add *Diluting solvent* to volume, and mix.~~

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~~*Procedure*—Concomitantly determine the absorbances of the *Assay preparation* and the *Standard preparation* in 1-cm cells at the wavelength of maximum absorbance at about 240 nm, with a suitable spectrophotometer, using *Diluting solvent* as the blank. Calculate the quantity, in mg, of $C_{11}H_{17}N_2NaO_3$ in the portion of Pentobarbital Sodium taken by the formula:~~

~~$$2.5C(248.26/226.28)(A_U/A_S),$$~~

~~in which *C* is the concentration, in µg per mL, of USP Pentobarbital RS in the *Standard preparation;* 248.26 and 226.28 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; and A_U and A_S are the absorbances of the *Assay preparation* and the *Standard preparation,* respectively.~~

■NOTE—Use the value for *Loss on drying* obtained at the same time as the preparation of the *Test solution* in the test for *Related compounds* and the *Assay preparation* in the *Assay.*■2S (*USP27*)

■*Mobile phase, Standard preparation,* and *Chromatographic system*—Proceed as described in the *Assay* under *Pentobarbital.*

Assay preparation—Transfer about 110 mg of Pentobarbital Sodium, accurately weighed, to a 100-mL volumetric flask, add about 80 mL of *Mobile phase,* and sonicate until dissolved. Dilute with *Mobile phase* to volume, and mix. Transfer 10.0 mL of this solution to a 100-mL volumetric flask. Dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the major peak. Calculate the quantity, in mg, of $C_{11}H_{17}N_2NaO_3$ in the portion of Pentobarbital Sodium taken by the formula:

$$(248.25/226.27)1000C(r_U/r_S),$$

in which 248.25 and 226.27 are the molecular weights of pentobarbital sodium and pentobarbital, respectively; *C* is the concentration, in mg per mL, of USP Pentobarbital RS in the *Standard preparation;* and r_U and r_S are the peak areas obtained from the *Assay preparation* and the *Standard preparation,* respectively.■1S (*USP27*)

BRIEFING

Pentoxifylline Extended-Release Tablets, page 3112 of the *Second Supplement*. In the table under *Tolerances* in *Drug release Test 2,* it is proposed to correct the 10-hour time point in accordance with the original documentation for this monograph.

(BPC: M. Marques) RTS—39974-1

Change to read:

■**Drug release** ⟨724⟩—

TEST 1—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 1.*
Medium: water; 900 mL or 1000 mL.
Apparatus 2: 100 rpm.
Times: 1, 4, 8, and 12 hours.
Procedure—Determine the amount of $C_{13}H_{18}N_4O_3$ dissolved by employing UV absorption at the wavelength of maximum absorbance at about 274 nm on filtered portions of the solution under test, suitably diluted with *Dissolution Medium,* if necessary, in comparison with a Standard solution having a known concentration of USP Pentoxifylline RS in the same *Medium.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to *Acceptance Table 1*.

Time (hours)	Amount dissolved
1	not more than 30%
4	between 30% and 55%
8	not less than 60%
12	not less than 80%

TEST 2—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 2.*
Medium: water; 900 mL.
Apparatus 2: 75 rpm.
Times: 1, 6, 10, and 20 hours.
Procedure—Proceed as directed under *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
1	between 8% and 30%
6	between 35% and 60%
10	between 53% and ~~80%~~ ■78%■2S (*USP27*)
20	not less than 80%

TEST 3—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 3.*
Medium: water; 900 mL.
Apparatus 1: 100 rpm.
Times: 2, 8, 12, and 20 hours.
Procedure—Proceed as directed under *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
2	between 15% and 35%
8	between 55% and 75%
12	between 75% and 95%
20	not less than 85%

TEST 4—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 4.*
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 1, 8, and 24 hours.
Procedure—Proceed as directed for *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
1	between 0% and 20%
8	between 35% and 60%
24	not less than 80%

TEST 5—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 5*.
Medium: water; 900 mL.
Apparatus 2: 75 rpm.
Times: 1, 2, 4, 6, and 20 hours.
Procedure—Proceed as directed for *Test 1,* except to use the wavelength of maximum absorbance at about 264 nm instead of 274 nm.
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
1	between 5% and 25%
2	between 10% and 35%
4	between 20% and 50%
6	between 30% and 60%
20	not less than 80%

TEST 6—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 6.*
Medium: simulated gastric fluid (without enzymes); 900 mL.
Apparatus 2: 50 rpm.
Times: 2, 8, 12, and 24 hours.
Procedure—Proceed as directed for *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
2	between 10% and 30%
8	between 40% and 60%
12	between 55% and 75%
24	not less than 85%

TEST 7—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 7.*
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 1, 3, 8, and 18 hours.
Procedure—Proceed as directed for *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
1	not more than 25%
3	between 25% and 45%
8	between 55% and 75%
18	not less than 80%

TEST 8—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 8.*
Medium: water; 900 mL.
Apparatus 2: 75 rpm.
Times: 1, 2, 4, 10, and 16 hours.
Procedure—Proceed as directed for *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
1	between 10% and 20%
2	between 15% and 35%
4	between 25% and 45%
10	between 55% and 75%
16	not less than 80%

TEST 9—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 9.*
Medium: water; 900 mL.
Apparatus 2: 50 rpm.
Times: 1, 3, 6, 12, and 18 hours.
Procedure—Proceed as directed for *Test 1,* except to use the wavelength of maximum absorbance at about 230 nm instead of 274 nm.
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
1	between 0% and 20%
3	between 20% and 40%
6	between 30% and 60%
12	between 50% and 80%
18	not less than 80%

TEST 10—If the product complies with this test, the labeling indicates that it meets USP *Drug Release Test 10.*
Medium: water; 900 mL.
Apparatus 2: 75 rpm.
Times: 1, 6, 12, and 20 hours.
Procedure—Proceed as directed for *Test 1.*
Tolerances—The percentages of the labeled amount of $C_{13}H_{18}N_4O_3$ dissolved at the times specified conform to the following table.

Time (hours)	Amount dissolved
1	not more than 20%
6	between 35% and 65%
12	between 60% and 90%
20	not less than 80% ■2S (*USP26*)

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BRIEFING

Perphenazine, *USP 26* page 1438—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-33

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Perphenazine RS. USP Perphenazine Sulfoxide RS.

Add the following:

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

BRIEFING

Perphenazine Oral Solution, *USP 26* page 1438—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-12

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Perphenazine Syrup, *USP 26* page 1439—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-13

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR SYRUP PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR SYRUP PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Phenobarbital, *USP 26* page 1448—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-34

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Phenobarbital RS.

Add the following:

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

BRIEFING

Phenylbutazone Injection, *USP 26* page 1457—See briefing under *Acepromazine Maleate.*

(VET: I. DeVeau) RTS—40270-16

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Phenylbutazone RS.

BRIEFING

Phenylephrine Hydrochloride, *USP 26* page 1459—See briefing under *Alfentanil Hydrochloride.*

(PA2: C. Anthony; PSD: C. Okeke) RTS—40356-1

Change to read:

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

■Store at 25°, excursions permitted between 15°and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Phenylephrine Hydrochloride RS.

Add the following:

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

BRIEFING

Phenytoin Oral Suspension, *USP 26* page 1466—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Saldado) RTS—40408-14

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Phenytoin Tablets, *USP 26* page 1467. It is proposed to change the title of this monograph to *Phenytoin Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40431-1

Phenytoin Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Phenytoin Chewable Tablets**

BRIEFING

Phenytoin Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40431-1

Add the following:

■Phenytoin Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Phenytoin Tablets)

» Phenytoin Chewable Tablets contain not less than 95.0 percent and not more than 105.0 percent of the labeled amount of $C_{15}H_{12}N_2O_2$.

Packaging and storage—Preserve in well-closed containers.

Labeling—Label the Chewable Tablets to indicate that they are to be chewed.

USP Reference standards ⟨11⟩—*USP Phenytoin RS.*

Identification—The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that of the major peak in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

0.05 M Tris buffer—Dissolve 60.5 g of tris(hydroxymethyl)aminomethane in 6 liters of water. Dilute with water to 10 liters, and adjust with phosphoric acid to a pH of 9.0 ± 0.05. Dissolve 100 g of sodium dodecyl sulfate in about 6 liters of the prepared buffer, transfer this solution to the remaining buffer solution, and mix.

Medium: 0.05 M Tris buffer; 900 mL.

Apparatus 2: 100 rpm.

Time: 120 minutes.

Determine the amount of $C_{15}H_{12}N_2O_2$ dissolved by employing the following method.

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Triethylamine solution, Mobile phase, and *Chromatographic system*—Proceed as directed in the *Assay.*

Standard solution—Dissolve an accurately weighed quantity of USP Phenytoin RS in methanol to obtain a solution having a known concentration of 3.0 mg per mL. Transfer a portion of this solution to a suitable container, and dilute quantitatively, and stepwise if necessary, with *Dissolution Medium* to obtain a concentration of 0.06 mg per mL. Transfer 10.0 mL of this solution to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test solution—Withdraw a portion of the solution under test, and filter, discarding the first 3 mL of the filtrate. Pipet 10.0 mL of this solution into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the peak responses. Determine the amount of $C_{15}H_{12}N_2O_2$ dissolved by comparison of the peak responses obtained from the *Standard solution* and the *Test solution*.

Tolerances—Not less than 70% (*Q*) of the labeled amount of $C_{15}H_{12}N_2O_2$ is dissolved in 120 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

Assay—

Triethylamine solution—Transfer 1 mL of triethylamine to a 100-mL volumetric flask, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of water, methanol, acetonitrile, *Triethylamine solution*, and acetic acid (500:270:230:5:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Phenytoin RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.5 mg per mL.

Assay preparation—Weigh and finely powder not fewer than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 250 mg of phenytoin, to a 500-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the column efficiency is not less than 6500 theoretical plates; the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{15}H_{12}N_2O_2$ in the portion of Chewable Tablets taken by the formula:

$$500C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of USP Phenytoin RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

(Official February 1, 2007)

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BRIEFING

Phenytoin Sodium, *USP 26* page 1467—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-35

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Phenytoin RS. ▲*USP Phenytoin Related Compound A RS.*
USP Phenytoin Related Compound B RS.▲*USP26*

Add the following:

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

BRIEFING

Physostigmine Salicylate, *USP 26* page 1473—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-36

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Physostigmine Salicylate RS.

Add the following:

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

BRIEFING

Potassium Iodide Oral Solution, *USP 26* page 1514—See briefing under *Acyclovir Oral Suspension.*

(PA7b: B. Davani) RTS—40399-3

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

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Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Povidone, *USP 26* page 1519 and page 1064 of *PF* 29(4) [July–Aug. 2003]. On the basis of comments received, it is proposed to reduce the current acceptable levels of Vinylpyrrolidinone in the test for *Vinylpyrrolidinone* from 2000 ppm to 10 ppm or less in order to minimize the safety risks associated with higher levels of the monomer. Also, it is proposed to replace the current titrimetric test for *Vinylpyrrolidinone* with an HPLC test published in the international harmonization Stage 5A draft proposal monograph. The proposed limit complies with both the harmonization Stage 5A draft proposal and the limit published in the European Pharmacopoeia. Interested parties are encouraged to comment.

(EMC: C. Sheehan) RTS—40407-1

Change to read:

» Povidone is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights. ~~It is characterized by its viscosity in aqueous solution, relative to that of water, expressed as a K-value, ranging from 10 to 120. The K-value of Povidone having a nominal K-value of 15 or less is not less than 85.0 percent and not more than 115.0 percent of the nominal K-value, and K-value of Povidone having a nominal K-value or nominal K-value range with an average of more than 15 is not less than 90.0 percent and not more than 108.0 percent of the nominal K-value or average of the nominal K-value range.~~

■The different types of Povidone are characterized by their viscosity in aqueous solution, relative to that of water, expressed as a K-value. (See the section on *K-value* below.) The K-value of Povidone having a stated (nominal) K-value of 15 or less is not less than 85.0 percent and not more than 115.0 percent of the stated values. The K-value of Povidone having a stated K-value or a stated K-value range with an average of more than 15 is not less than 90.0 percent and not more than 108.0 percent of the stated value or of the average of the stated range.■1S (*USP27*)

Change to read:

Limit of aldehydes—

Phosphate buffer—Transfer ~~50.0 g~~ ■8.3 g■1S (*USP27*) of potassium pyrophosphate to a 500-mL volumetric flask, and dissolve in 400 mL of water. Adjust, if necessary, with 1 N hydrochloric acid to a pH of 9.0, dilute with water to volume, and mix.

Aldehyde dehydrogenase solution—Transfer a quantity of lyophilized aldehyde dehydrogenase equivalent to 70 units to a glass vial, dissolve in 10.0 mL of water, and mix. [NOTE—This solution is stable for 8 hours at 4°.]

NAD solution—Transfer 40 mg of nicotinamide adenine dinucleotide to a glass vial, dissolve in 10.0 mL of *Phosphate buffer*, and mix. [NOTE—This solution is stable for 4 weeks at 4°.]

Standard preparation—Add about 2 mL of water to a glass weighing bottle, and weigh accurately. Add about 100 mg (about 0.13 mL) of freshly distilled acetaldehyde, and weigh accurately. Transfer this solution to a 100-mL volumetric flask. Rinse the weighing bottle with several portions of water, transferring each rinsing to the 100-mL volumetric flask. Dilute the solution in the 100-mL volumetric flask with water to volume, and mix. Store at 4° for about 20 hours. Pipet 1 mL of this solution into a 100-mL volumetric flask, dilute with water to volume, and mix.

Test preparation—Transfer about 2 g of Povidone, accurately weighed, to a 100-mL volumetric flask, dissolve in 50 mL of *Phosphate buffer,* dilute with *Phosphate buffer* to volume, and mix. Insert a stopper into the flask, heat at 60° for 1 hour, and cool to room temperature.

Procedure—Pipet 0.5 mL each of the *Standard preparation,* the *Test preparation,* and water to provide the reagent blank into separate 1-cm cells. Add 2.5 mL of *Phosphate buffer* and 0.2 mL of *NAD solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 2 to 3 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Add 0.05 mL of *Aldehyde dehydrogenase solution* to each cell. Cover the cells to exclude oxygen. Mix by inversion, and allow to stand for 5 minutes at 22 ± 2°. Determine the absorbances of the solutions at a wavelength of 340 nm, using water as the reference. Calculate the percentage of aldehydes, expressed as acetaldehyde, in the portion of Povidone taken by the formula:

$$10(C/W)\left[\frac{(A_{U2}-A_{U1})-(A_{B2}-A_{B1})}{(A_{S2}-A_{S1})-(A_{B2}-A_{B1})}\right],$$

in which C is the concentration, in mg per mL, of acetaldehyde in the *Standard preparation; W* is the weight, in g, of Povidone taken; A_{U1}, A_{S1}, and A_{B1} are the absorbances of the solutions obtained from the *Test preparation,* the *Standard preparation,* and the water reagent blank, respectively, before addition of the *Aldehyde dehydrogenase solution;* and A_{U2}, A_{S2}, and A_{B2} are the absorbances of the solutions obtained from the *Test preparation,* the *Standard prepa-*

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ration, and the water reagent blank, respectively, after addition of the *Aldehyde dehydrogenase solution:* not more than 0.05% is found.

Change to read:

Vinylpyrrolidinone—~~Dissolve 10.0 g of Povidone in 80 mL of water, add 1.0 g of sodium acetate, and titrate with 0.10 N iodine until the color of iodine no longer fades. Add an additional 3.0 mL of 0.10 N iodine, allow to stand for 10 minutes, and titrate the excess iodine with 0.10 N sodium thiosulfate, adding 3 mL of starch TS as the endpoint is approached. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩), using the same total volume of 0.10 N iodine, accurately measured, as was used for titrating the specimen: not more than 3.6 mL of 0.10 N iodine is consumed, corresponding to not more than 0.2% of vinylpyrrolidinone.~~

■*Mobile phase*—Prepare a mixture of methanol and water (20:80).

System suitability solution—Transfer 10 mg of vinylpyrrolidinone and 500 mg of vinyl acetate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with methanol to volume. Transfer 1.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Standard preparation—Transfer an accurately weighed quantity of 50 mg of vinylpyrrolidinone to a 100-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 1.0-mL of this solution to a 100-mL volumetric flask, dilute with methanol to volume, and mix. Transfer 5.0 mL of this solution to a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Test preparation—Transfer an accurately weighed quantity of about 250 mg of Povidone to a 10-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 235-nm detector, a 4.0-mm × 2.5-cm guard column containing packing L7, and a 4.0-mm × 25-cm analytical column containing 5-µm packing L7. The column temperature is maintained at about 40°. Adjust the flow rate so that the retention time of vinylpyrrolidinone is about 10 minutes. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between vinylpyrrolidinone and vinyl acetate is not less than 2.0. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separetely inject equal volumes (about 50 µL) each of the *Standard preparation* and the *Test preparation* into the chromatograph, record the chromatograms, and measure the responses for the vinylpyrrolidinone peak. [NOTE—If necessary, after each injection of the *Test preparation,* wash the polymeric material of Povidone from the guard column by passing the *Mobile phase* through the column backwards for about 30 minutes at the same flow rate.] Calculate the percentage of vinylpyrrolidinone in the sample taken by the formula:

$$1000\ (C/W)\ (r_U / r_S),$$

in which C is the concentration, in mg per mL , of vinylpyrrolidinone in the *Standard preparation; W* is the weight , in mg, of Povidone taken to prepare the *Test preparation;* and r_U and r_S are the peak responses for vinylpyrrolidinone obtained from the *Test preparation* and *Standard preparation,* respectively: not more than 0.001 % is found.■2S (*USP27*)

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BRIEFING

Primidone Oral Suspension, *USP 26* page 1539—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-15

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Prochlorperazone Oral Solution, *USP 26* page 1550—See briefing under *Dihydrotachysterol Oral Solution.*

(PA4: E. Gonikberg) RTS—40419-6

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Propofol, page 1854 of *PF* 28(6) [Nov.–Dec. 2002]. On the basis of comments received, the following revisions are proposed, and, where possible, procedures are harmonized to the *EP* monograph for Propofol:

- A revision is proposed to the *Packaging and storage* statement to specify packaging in light-resistant containers under inert gas; the recommended storage temperature is specified in accordance with the USP Packaging, Storage, and Distribution (PSD) Expert Committee.
- Two reference standards, USP Propofol for System Suitability RS and USP Propofol Related Compound B RS, are added to support proposed analytical procedures, and it is proposed to designate 3,3′,5,5′-Tetraisopropyldiphenol as USP Propofol Related Compound A RS.
- A narrower specification is proposed for the test for *Refractive index;* the range is in agreement with that in the *EP* monograph.
- Purification by distillation renders the tests for *Water, Residue on ignition, Heavy metals,* and *Content of chloride* unnecessary; the deletion of these tests is proposed, again, in accordance with the *EP* monograph.
- Deletion is proposed for the test for *Bacterial endotoxins* because the finished product specification will control the amount of endotoxins.
- In order to accommodate detection and quantitation of propofol and impurities resulting from different synthetic processes, the *Chromatographic purity* test is being renamed to *Related compounds* and an additional test, *Test 2,* is added; the *Limit of 3,3′-5,5′-tetraisopropyldiphenol* is renamed to *Limit of propofol related compound A;* the *Limit of 2,6-diisopropylbenzoquinone* is renamed to *Limit of propofol related compound B* with the addition of another test, *Test 2;* and in the *Assay,* another test is added. These proposed normal phase HPLC procedures are based on those in the *EP* monograph for Propofol; use of a Partisil column is recommended, and propofol elutes at about 3 minutes.
- It is proposed to revise the *Labeling* statement to indicate which *Related compounds* procedure is used.
- A revision is proposed to the *Limit of propofol related compound A* procedure to eliminate the use of propofol and change the solvent to methanol.
- A new procedure is proposed for *Test 1* in the *Assay,* replacing the current method that uses a G49 column. Advantages of the proposed procedure include the following: (1) increased laboratory efficiency because it uses the same column (G16) and carrier gas (helium) as in *Related compounds Test 1;* (2) elimination of methylene chloride as the solvent in favor of methanol; and (3) increased precision because the procedure does not use a split-flow technique. The validation was performed using an AT-Wax brand of G16 column; propofol elutes between 14 and 16 minutes on this system.
- Minor editorial changes are also proposed.

(PA1: K. Russo; PSD: C. Okeke; NL: C. Barnstein) RTS—39437-1; 39468-2; 40025-1; 40225-1; 40393-1

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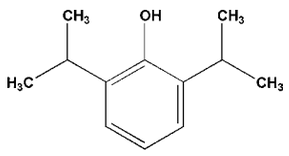
Add the following:

■Propofol



$C_{12}H_{18}O$ 178.27

Phenol, 2,6-bis(1-methylethyl).

2,6-Diisopropylphenol [*2078-54-8*].

» Propofol contains not less than 98.0 percent and not more than 102.0 percent of $C_{12}H_{18}O$. ~~calculated on the anhydrous basis.~~

Packaging and storage—~~Preserve in tight containers.~~ Preserve in tight, light-resistant containers under an atmosphere of inert gas. Store at 25°, excursions permitted between 15° and 30°.

Labeling—

The labeling indicates the *Related compounds* test with which the article complies.

USP Reference standards ⟨11⟩—*USP Propofol RS. USP Propofol Resolution RS.* ~~*USP 3,3′-5,5′-Tetraisopropyldiphenol RS.*~~ *USP Propofol Related Compound A RS. USP Propofol Related Compound B RS. USP Propofol for System Suitability RS.*

Identification, *Infrared Absorption* ⟨197F⟩.

Refractive index ⟨831⟩: between ~~1.5120 and 1.5160~~ 1.5125 and 1.5145 at 20°.

~~**Bacterial endotoxins** ⟨85⟩: [To come.]~~

~~**Water,** *Method Ia* ⟨921⟩: not more than 0.20%.~~

~~**Residue on ignition** ⟨281⟩: not more than 0.10%.~~

~~**Heavy metals,** *Method II* ⟨231⟩: 0.002%.~~

~~**Chromatographic purity**—~~

Related compounds—[NOTE—Based on knowledge of the manufacturing process, either (1) *Related compounds Test 1* is performed in conjunction with the *Limit of propofol related compound A, Limit of propofol related compound B Test 1,* and *Assay Test 1* procedures, or (2) *Related compounds Test 2* is performed in conjunction with the *Limit of propofol related compound B Test 2* and the *Assay Test 2* procedures.]

~~*System suitability solution* and *Chromatographic system*—Proceed as directed in the *Assay.*~~

~~*Test solution*—Use the *Assay preparation.*~~

~~*Procedure*—Inject equal volumes (about 0.5 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:~~

~~$100(r_i/r_s)$,~~

~~in which r_i is the peak response for each impurity obtained from the *Test solution;* and r_s is the peak response for propofol obtained from the *System suitability solution:* not more than 0.3% of any individual impurity is found; and not more than 1.0% of total impurities is found.~~

~~*System suitability solution*—Prepare a solution in dichloromethane containing 4 µg of 2-isopropylphenol and 4 mg of USP Propofol RS per mL.~~

~~*Test solution*—Dissolve 400 mg of Propofol in 100 mL of dichloromethane, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.25-mm × 30-m column coated with a 0.15-mm phase G3, and a 0.53-mm × 5-m deactivated fused-silica guard column. The carrier gas is helium, flowing at a rate of about 1.7 mL per minute and maintained at about 20 psi. The detector temperature is maintained at 270°. The injector~~

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~~temperature is maintained at 38°; immediately after the injection it is increased at a rate of 125° per minute to 270°; and then it is maintained at 270° for 28 minutes. Initially the temperature of the column is equilibrated at 35° for 3 minutes; upon injection it is increased at a rate of 20° per minute to 80°; it is increased again at a rate of 6° per minute to 150°; it is increased again at a rate of 20° per minute to 270°; and then it is maintained at 270° for 7 minutes. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure*: the relative retention times are about 0.8 for 2-isopropylphenol and 1.0 for propofol; the tailing factor for the 2-isopropylphenol peak is not more than 2; the peak area for 2-isopropylphenol is not less than 0.085% and not more than 0.125% relative to propofol; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*— Separately inject equal volumes (about 5 µL) of the *System suitability solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure all the peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:~~

~~$100(r_i/r_u)$,~~

~~in which r_i is the peak response for each impurity obtained from the *Test solution;* and r_u is the sum of the responses for all the peaks, excluding that of the solvent peak: not more than 0.1% of any individual peak is found; and not more than 0.3% of total impurities is found.~~

TEST 1—

Resolution solution— ~~Dissolve about 1000 mg of USP Propofol Resolution RS in 10.0 mL of methanol.~~Dissolve an accurately weighed quantity of USP Propofol ~~Resolution~~ RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of about 100 mg per mL.

Standard solution— ~~Dissolve 50 mg of USP Propofol RS in 50.0 mL of methanol, and mix. Further dilute 5.0 mL of this solution with methanol to 50.0 mL.~~Dissolve an accurately weighed quantity of USP Propofol RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of about 0.1 mg per mL.

Test solution— ~~Dissolve 1000 mg of Propofol in 10.0 mL of methanol.~~Transfer about 1000 mg of Propofol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with methanol to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)— ~~The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m column coated with a 1.2-µm phase G16. The carrier gas is helium, flowing at a rate of about 8 mL per minute. The injection port and the detector temperatures are maintained at 250° and 300°, respectively. The chromatograph is programmed as follows. Upon injection, the column temperature is maintained at 145° for 20 minutes; the temperature is increased at a rate of 5° per minute to 200° and maintained at 200° for 5 minutes. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:*~~ Proceed as directed under *Assay Test 1,* except to chromatograph the *Standard solution* six times and chromatograph the *Resolution solution:* the relative retention time is about 0.18 for 2,6-diisopropylphenyl isopropylether, 1.0 for propofol, and about 1.1 for 2-isopropyl-6-*n*-propylphenol; the resolution, *R,* between propofol and 2-isopropyl-6-*n*-propylphenol is not less than 2. Chromatograph the *Standard solution* six times, and record the peak responses as directed for *Procedure:* the column efficiency determined from the propofol peak is not less than 5000 theoretical plates; and the relative standard deviation for replicate injections is not more than 3.5%.

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Procedure—Separately inject equal volumes (about 1.0 µL) of the *Resolution solution, Standard solution,* and *Test solution* into the chromatograph, record the chromatograms, and measure all of the peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:

$$0.1(r_i / r_S),$$

in which r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for propofol obtained from the *Standard solution:* not more than 0.1% of 2,6-diisopropylphenyl isopropylether is found; not more than 0.1% of each other individual impurity is found; and not more than 0.3% of total impurities is found.

TEST 2—

Mobile phase—Prepare as directed in *Assay Test 2.*

System suitability solution 1—Transfer 5 µL of USP Propofol RS and 15 µL of USP Propofol Related Compound B RS to a 50-mL volumetric flask, dissolve in and dilute with hexane to volume, and mix

System suitability solution 2—Dissolve 1 mL of USP Propofol for System Suitability RS with hexane to make 10 mL.

Test solution—Transfer about 1000 mg of Propofol, accurately weighed, to a 10-mL volumetric flask, dissolve in and dilute with hexane to volume, and mix.

Reference solution—Dilute 1 mL of the *Test solution* with hexane to 100 mL, and mix. Dilute 1 mL of this solution with hexane to 10 mL, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed in *Assay Test 2.* Chromatograph *System suitability solution 1* and *System suitability solution 2,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.8 for propofol related compound B from *System suitability solution 1,* and 0.5 for 2-(1-methylethoxy)-1,3-bis(1-methylethylbenzene), 1.0 for propofol, and 5.0 for propofol related compound A from *System suitability solution 2;* the resolution, *R,* between propofol related compound B and propofol is at least 4.0.

Procedure—Separately inject a volume (about 10 µL) of the *Test solution* and *Reference solution* into the chromatograph, record the chromatogram, and measure all peak responses. Calculate the percentage of each impurity in the portion of Propofol taken by the formula:

$$0.1(r_i / r_S)(1/F),$$

in which r_i is the peak response for each impurity obtained from the *Test solution;* r_S is the peak response for propofol obtained from the *Reference solution;* and F is the response factor. F is 0.2 for 2,6-diisopropylphenylisopropyl ether and 4.0 for propofol related compound A: not more than 0.2% of 2-(1-methylethoxy)-1,3-bis(1-methylethylbenzene) is found; not more than 0.2% of 2,6-diisopropylphenylisopropyl ether is found; not more than 0.01% of propofol related compound A is found; not more than 0.05% of each other individual impurity is found; and not more than 0.3% of total impurities is found.

Limit of ~~3,3′-5,5′-tetraisopropyldiphenol~~ propofol related compound A—[NOTE—This is to be performed in conjunction with *Related compounds Test 1.*]

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile, water, and methanol (50:40:10).

Standard solution—Prepare a solution in ~~*Mobile phase*~~ methanol containing ~~2~~ 20 µg per mL ~~each~~ of ~~USP Propofol RS and USP 3,3′-5,5′-Tetraisopropyldiphenol RS.~~ USP Propofol Related Compound A RS.

Test solution—~~Dissolve 500 mg of Propofol in 25.0 mL of *Mobile phase.*~~ Transfer about 500 mg of Propofol, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with ~~*Mobile phase*~~ methanol to volume, and mix.

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Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 270-nm detector and a 4.6-mm × 15-cm column that contains packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard solution* six times, and record the peak responses as directed for *Procedure:* the column efficiency, based on the ~~propofol~~ propofol related compound A peak, is not less than 6000 theoretical plates; and the relative standard deviation for replicate injections for ~~propofol and 3,3′-5,5′-tetraisopropyldiphenol~~ propofol related compound A peaks is not more than 15%.

Procedure—Separately inject equal volumes (about 20 mL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses for ~~3,3′-5,5′-tetraisopropyldiphenol~~ propofol related compound A. Calculate the percentage of ~~3,3′-5,5′-tetraisopropyldiphenol~~ propofol related compound A in the portion of Propofol taken by the formula:

$$~~0.01(r_U/r_S),~~$$

$$0.01(r_U/r_S),$$

in which ~~r_U~~ r_U and r_S are the peak responses for ~~3,3′-5,5′-tetraisopropyldiphenol~~ propofol related compound A obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.1% of ~~3,3′-5,5′-tetraisopropyldiphenol~~ propofol related compound A is found.

Limit of ~~2,6-diisopropylbenzoquinone~~ propofol related compound B—

TEST 1—[NOTE—This is to be performed in conjunction with *Related compounds Test 1.*]

Sample solution: neat.

Procedure—Examine the portion of Propofol taken at 330 nm using air as the blank (see *Ultraviolet Absorption* ⟨197U⟩. The absorbance of the *Sample solution* is not more than 0.4 absorbance units (0.1%).

TEST 2—[NOTE—This is to be performed in conjunction with *Related compounds Test 2.*]

Mobile phase—Prepare as directed under *Assay Test 2.*

Stock standard solution—Dissolve about 5 mg of USP Propofol Related Compound B RS in hexane, and dilute with hexane to 50 mL.

Standard solution—Dilute 5 mL of the *Stock standard solution* with hexane to 100 mL.

Test solution—Dissolve about 0.5 g of Propofol in hexane, and dilute with hexane to 10 mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed under *Assay Test 2* except that the liquid chromatograph is equipped with a detector at 254 nm. Chromatograph the *Standard solution* and the *Test solution,* and record the peak responses as directed for *Procedure:* the relative retention time for propofol related compound B is about 0.8 and 1.0 for propofol.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of propofol related compound B in the portion of Propofol taken by the formula:

$$100(C_S/C_U)(r_U/r_S),$$

in which C_S is the concentration, in mg per mL, of the *Standard solution;* C_U is the concentration, in mg per mL, of propofol in the *Test solution;* and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 0.05% of propofol related compound B is found.

~~**Content of chloride** ⟨221⟩—Dissolve about 3 g of Propofol, accurately weighed, in 60 mL of methanol, add 10 mL of water and 20 mL of 2 N nitric acid, and titrate with 0.01 N silver nitrate VS, determining the endpoint potentiometri-~~

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~~cally (see *Titrimetry* ⟨541⟩). Each mL of 0.01 N silver nitrate is equivalent to 35.45 0.3545 mg of chloride: not more than 0.01% of chloride is found.~~

Assay—

~~*System suitability solution*—Dissolve about 100 mg of USP Propofol RS and 10 mg of triethylamine in 5.0 mL of dichloromethane, and mix.~~

~~*Standard preparation*—Dissolve 100 mg of USP Propofol RS in 5.0 mL of dichloromethane, and mix.~~

~~*Assay preparation*—Dissolve 100 mg of Propofol in 5.0 mL of dichloromethane, and mix.~~

~~*Chromatographic system* (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.25-mm × 30-m column coated with a 0.25-µm phase G49. The carrier gas is hydrogen, flowing at a rate of about 2 mL per minute and maintained at 10 psi; and the split flow rate is about 10 mL per minute with a split flow ratio of 5:4. The injection port and the detector temperatures are maintained at 250° and 300°, respectively. The chromatograph is programmed as follows. Initially the column temperature is equilibrated at 60° for 2 minutes; upon injection the temperature is increased at a rate of 10° per minute to 150°; the temperature is increased again at a rate of 30° per minute to 270°; and is maintained at 270° for 5 minutes. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.15 for triethylamine and 1.0 for propofol; and the relative standard deviation for replicate injections is not more than 2.0%.~~

~~*Procedure*—Separately inject equal volumes (about 0.5 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{12}H_{18}O$, in the portion of Propofol taken by the formula:~~

$$5C(r_U/r_S),$$

~~in which *C* is the concentration, in mg per mL, of USP Propofol RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.~~

TEST 1—[NOTE—This is to be performed in conjunction with *Related compounds Test 1.*]

Standard preparation—Dissolve an accurately weighed quantity of USP Propofol ~~System Suitability~~ Resolution RS in methanol, and dilute quantitatively, and stepwise if necessary, with methanol to obtain a solution having a concentration of about 10 mg per mL.

Assay preparation—Transfer about 250 mg of Propofol, accurately weighed, to a 25-mL volumetric flask, dissolve in and dilute with methanol to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm × 30-m column coated with a 1.2-µm phase G16. The carrier gas is helium, flowing at a rate of about 8 mL per minute. The injection port and the detector temperatures are maintained at 250° and 300°, respectively. The chromatograph is programmed as follows. Upon injection, the column temperature is maintained at 145° for 20 minutes; the temperature is increased at a rate of 5° per minute to 200° and maintained at 200° for 5 minutes. Chromatograph the *Standard preparation* five times, and record the peak responses as directed for *Procedure:* the column efficiency determined from the propofol peak is not less than 5000 theoretical plates; the tailing factor is not more than 2.5; and the relative standard deviation for replicate injections is not more than 1.5%.

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Procedure—Separately inject equal volumes (about 1.0 µL) of the *Standard preparation* and *Assay preparation* into the chromatograph, record the chromatograms, and measure the peak responses for the major peaks. Calculate the percentage of $C_{12}H_{18}O$ in the portion of Propofol taken by the formula:

$$100(C_S / C_U)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Propofol RS in the *Standard preparation;* C_U is the concentration, in mg per mL, of propofol in the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

TEST 2—[NOTE—This is to be performed in conjunction with *Related compounds Test 2.*]

Mobile phase—Prepare a filtered and degassed mixture of hexane, acetonitrile, and ethanol (990:7.5:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Propofol RS in hexane, and dilute quantitatively, and stepwise if necessary, with hexane to obtain a solution having a concentration of about 2.4 mg per mL

Assay preparation—Transfer about 240 mg of Propofol, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with hexane to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 275-nm detector and ~~4.9~~ 4.6-mm × 20-cm column that contains 5-µm packing L3. The flow rate is about 2 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not more than 1.5; and the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for the propofol peaks. Calculate the quantity, in mg, of $C_{12}H_{18}O$ in the portion of Propofol taken by formula:

$$100(C_S / C_U)(r_U / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Propofol RS in the *Standard preparation;* C_U is the concentration, in mg per mL, of propofol in the *Assay preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Propyliodone, *USP 26* page 1584—See briefing under *Adenosine.*

(RMI: A. Wilk) RTS—40329-19

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

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Add the following:

■**Other requirements—**Where the label states that Propyliodone is sterile, it meets the requirements under *Sterility Tests* ⟨71⟩.■2S (*USP27*)

BRIEFING

Pyrantel Pamoate Oral Suspension, *USP 26* page 1595—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-4

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Pyridostigmine Bromide, *USP 26* page 1597—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-37

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Pyridostigmine Bromide RS.

Add the following:

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

BRIEFING

Pyrvinium Pamoate Oral Suspension, *USP 26* page 1603—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-5

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Saquinavir Mesylate, *USP 26* page 1664. On the basis of new information received, in the test for *Heavy metals* it is proposed to use *Method II* instead of *Method I* and to revise the limit.

(PA7b: B. Davani) RTS—39797-1

Change to read:

Heavy metals, ~~*Method I*~~

■*Method II*■2S (*USP27*)
⟨231⟩—Dissolve 2.5 g in 50 mL of a mixture of alcohol and water (7:1): the limit is ~~0.002%.~~

■0.001%.■2S (*USP27*)

BRIEFING

Secobarbital Sodium, *USP 26* page 1671—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-38

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

BRIEFING

Sodium Citrate and Citric Acid Oral Solution, *USP 26* page 1694—See briefing under *Chlorothiazide Oral Suspension.*

(PA5: A. Wilk) RTS—40368-6

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Somatropin; Somatropin for Injection. Since the publication of the proposed monograph of Somatropin in *PF* 25(4), many comments were received from manufacturers of the product; therefore, the original proposal is canceled and a new monograph is proposed on the basis of those comments. The revisions and the justifications are summarized below.

1. **Identification test C:** *Electrophoretic Test*
   The test has been deleted because (a) it is difficult to reproduce and (b) the results are not consistent from manufacturer to manufacturer. In addition, several problems with the details of the procedure were reported. Furthermore, the need for this test was questioned because there were two other identification tests included in the proposed monograph—a chromatographic identity test and a test for peptide mapping.
2. **Limit of high molecular weight of proteins**
   The procedure for this test is the same as that of the procedure for the *Assay*, except for the injection volume. A suggestion was made to change the injection volume to 20 µL to make it consistent with the *Assay* procedure.
3. **Chromatographic purity**
   - The requirement for a limit for any individual impurity is deleted. In the proposed monograph published in *PF* 25(4), the acceptance criteria of this test were not more than 2.0% of any individual impurity and not more than 6.0% of total impurities. It was suggested that the requirement of the individual impurity should be removed because of lack of appropriate resolution of the desamido peak from its adjacent peak and because multiple desamido peaks overlap with other impurities. Deleting the requirement for any individual impurity also is consistent with the somatropin monograph in the *European Pharmacopeia* (*EP*).
   - The system suitability requirement in terms of an absolute retention time of the somatropin peak is deleted. In the proposed monograph published in *PF* 25(4), a retention time for the somatropin peak between 30.0 and 36.6 minutes was suggested as part of the system suitability requirement. However, because the absolute retention time can vary significantly from column to column, an absolute retention time is inappropriate as a system suitability requirement. An evaluation in the USP laboratory supports this observation. It was shown that when L26 columns from different manufacturers were used, there

was a significant variation in the retention time, with values extending beyond the limits specified in the proposed monograph (30.0–36.6 minutes). However, it is desirable that the system suitability should include acceptance criteria in terms of a relative retention time of the somatropin peak either with respect to an internal or an external standard. The manufacturers are encouraged to submit proposals for such a revision.

4. **Cell proliferation bioactivity test**
The *Cell proliferation* test is deleted.
   - The proposed monograph published in *PF* 25(4) included the cell proliferation test as one of the bioactivity tests, which requires the use of cells that were specially made for the test by genetic engineering . To obtain those cells, the manufacturers would have to sign a restricted-use agreement with USP. The company that developed the cells for this assay for USP required USP to set the condition that USP would make the cells available only to those manufacturers who would sign such an agreement. Many manufacturers of somatropin informed USP that signing such an agreement is inappropriate and might be detrimental to their business interest. Accordingly, USP proposed to withdraw the *Cell proliferation* test as one of the bioactivity tests.
   - On the basis of the results of an international collaborative study (European Pharmacopoeia Commission. *Pharmeuropa,* Vol. 3, Special Issue, March 1991), in 1993, the bioassays were deleted from the *EP* somatropin monograph. The study showed that the bioassay could be removed from the monograph without compromising the safety and quality of the product. The study concluded, "the in-vivo bioassay remains essential during product development and validation of the manufacturing process. However, once a manufacturing process and its product have been validated and shown to be consistent, then on-going batch testing and product monitoring to ensure safety and efficacy can be undertaken using a battery of physicochemical tests sufficient to guarantee identity, purity, and amount (vial content) within set specification limits." Such physicochemical procedures "include reverse-phase liquid chromatography and size-exclusion chromatography", and are included in the current revision.

5. **Rat weight-gain test**
In the Somatropin monograph published in *PF* 25(4), the rat weight-gain test was included as a bioactivity test. In the current proposal the test is proposed as a test for *Bioidentity.*
   - The data obtained from manufacturers indicate that the rat weight-gain test has significantly large variability. Thus, the test is not suitable as a bioactivity test. However, the test would be suitable as a bioidentity test.
   - Several manufacturers questioned the need for this test as a bioidentity test because it involves a significant amount of effort, not generally warranted for a bioidentity test. Unfortunately, at present, there is no good bioassay available for somatropin that can be used by everyone "without strings attached." Furthermore, the USP Biotechnology and Natural Therapeutics and Diagnostics Expert Committee determined that it would be inappropriate to have a growth hormone protein monograph without any test to ensure that it is biologically active. However, the manufacturers are not required to perform the test on every lot, provided that lot-to-lot consistency has been demonstrated through adequate historical data and through process validation (see *General Notices*).

6. **USP Reference standards**
The requirement of USP F1 Cells for Cell Proliferation Test RS is deleted because this Reference Standard was related to the test for *Cell proliferation*, which is no longer in the new proposal.

7. **Assay**
   - The system suitability requirement in terms of an absolute retention time of the somatropin peak is deleted. The proposed monograph published in *PF* 25(4) suggested a retention time for the somatropin peak between 12 and 17 minutes as part of the system suitability requirement. This requirement is deleted for reasons similar to those described above under *Chromatographic purity* test.
   - The word "potency" is changed to "quantity". The assay procedure is physicochemical, i.e., it measures the "quantity" of somatropin in mg, not its bioactivity. On the other hand, "potency" is related to bioactivity and is measured in USP Somatropin Units (or in IU of Somatropin). However, as mentioned above under the *Cell proliferation bioactivity test,* the *Assay* correlates to the bioactivity, that is, potency, of somatropin.

(BNT: L. Bhattacharyya) RTS—40028-1

Add the following:

■Somatropin

FPTIPLSRLF DNAMLRAHRL HQLAFDTYQE FEEAYIPKEQ KYSFLQNPQT
SLCFSESIPT PSNREETQQK SNLELLRISL LLIQSWLEPV QFLRSVFANS
LVYGASDSNV YDLLKDLEEG IQTLMGRLED GSPRTGQIFK QTYSKFDTNS
HNDDALLKNY GLLYCFRKDM DKVETFLRIV QCRSVEGSCG F

$C_{990}H_{1528}N_{262}O_{300}S_7$ 22,125.19 [*12629-01-5*].

» Somatropin is a protein hormone consisting of 191 amino acid residues, and its structure corresponds to the major component of the growth hormone extracted from human pituitary glands. It is produced by methods based on recombinant DNA technology. When prepared as a lyophilized powder, it contains not less than 910 µg of somatropin per mg, calculated on the anhydrous basis. When prepared as a bulk solution, it contains not less than 910 µg of somatropin per mg of total protein. The presence of host-cell DNA and host-cell protein impurities in Somatropin is process specific—the limits of these impurities are determined by validated methods. Manufacturers must exhibit a

correlation between the *Assay* and a validated and approved growth-promotion based bioassay. It may contain excipients. [NOTE—One mg of anhydrous Somatropin is equivalent to 3.0 USP Somatropin Units.]

Packaging and storage—Preserve in tight containers, and store between –10° and –25°.

Labeling—The labeling states that the material is of recombinant DNA origin.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Somatropin RS.*

Identification—

A: Proceed as directed in the test for *Chromatographic purity,* except to prepare a *Standard solution* by reconstituting a vial of USP Somatropin RS with the *Diluent* to obtain a solution having a known concentration of about 2.0 mg per mL. Chromatograph the *Standard solution* and the *Test solution* as directed for *Procedure:* the retention time of the somatropin peak in the chromatogram of the *Test solution* corresponds to that in the chromatogram of the *Standard solution*.

B: *Peptide Mapping* (see *Biotechnology-Derived Articles—Tests* ⟨1047⟩)—

Solution A—Prepare a filtered and degassed solution of trifluoroacetic acid in water (1 in 1000, v/v).

Solution B—Transfer 100 mL of water to a 1000-mL volumetric flask, add 1 mL of trifluoroacetic acid, dilute with acetonitrile to volume, and mix.

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments to either solution as necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Tris buffer—Prepare a 0.05 M solution of tris(hydroxymethyl)aminomethane (Tris), and adjust with hydrochloric acid to a pH of 7.5.

Trypsin solution—Prepare a solution containing 1 mg of trypsin per mL of *Tris buffer,* and mix. Store in a freezer, if necessary.

Standard solution—Prepare a solution containing 2.0 mg of USP Somatropin RS per mL of the *Tris buffer,* and mix. Add 1 mL of this solution to a suitable tube, and add 30 µL of *Trypsin solution*. Cap the tube, and place it in a water bath at 37° for 4 hours. [NOTE—If this solution is not injected immediately, store it in a freezer.]

Test solution—Prepare a solution containing 2.0 mg of Somatropin per mL of *Tris buffer,* and mix. Add 1 mL of this solution to a suitable tube, and add 30 µL of *Trypsin solution.* Cap the tube, and place it in a water bath at 37° for 4 hours. [NOTE—If this solution is not injected immediately, store it in a freezer.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains packing L7. The flow rate is 1 mL per minute and the column temperature is maintained at 30°. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0→20	100→80	0→20	Linear gradient
20→40	80→75	20→25	Linear gradient
40→65	75→50	25→50	Linear gradient
65→70	50→20	50→80	Linear gradient
70→71	20→100	80→0	Linear gradient
71→86	100	0	Isocratic, re-equilibration

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Procedure—[NOTE—Condition the chromatographic system by running a blank gradient program prior to injecting the digests.] Separately inject equal volumes (about 100 µL) of the *Standard solution* and the *Test solution,* and record the chromatograms: the chromatographic profile of the *Test solution* is similar to that of the *Standard solution*.

Bioidentity—

Buffer solution—Prepare a solution of 0.1 M ammonium bicarbonate, and adjust with sodium hydroxide to a pH of 8.0.

Standard solutions—Transfer accurately weighed quantities of USP Somatropin RS, and dissolve in and dilute quantitatively with *Buffer solution* to obtain solutions having known concentrations between 10 and 100 µg per mL.

Test solutions—Transfer accurately weighed amounts of Somatropin, and dissolve in and dilute quantitatively with *Buffer solution* to obtain solutions with concentrations similar to those of the *Standard solutions*. [NOTE—Do not agitate while mixing; swirl gently.]

Control solution—Use the *Buffer solution*.

Test animals—Select an appropriate number of only female or only male Sprague Dawley rats hypophysectomized at 25 to 30 days of age. After hypophysectomization, feed the rats on rat chow and 5% sucrose water for at least 72 hours. After 72 hours, feed the rats on rat chow and filtered and deionized water adjusted with 1 N hydrochloric acid to a pH of 3.0 ± 0.25. Weigh the rats when they are 37 to 44 days old, and retain only healthy rats. Reweigh the remaining rats 7 days later, and use only those rats that are in good health and have not gained or lost more than 10% of their body weight in the previous 7-day period.

Procedure— Randomly divide the rats into Control, Standard, and Test groups, each group containing approximately 10 rats. Each day for 10 days inject subcutaneously 0.1 mL of the *Control solution, Standard solutions,* and *Test solutions* to the Control, Standard, and Test groups, respectively. Record the body weight of each animal at the start of the test and at approximately 18 hours following the 10th injection. Determine the change in body weight for each rat during the 10-day period, and compute the potency of the *Test solution* relative to that of the *Standard solution* using appropriate statistical analysis. Calculate the mean potency in USP Somatropin Units per mg: not less than 2 USP Somatropin Units per mg is found. Using appropriate statistical methods, calculate the width, *L,* of a 95% confidence interval for the estimated logarithm of the relative potency: *L* is not more than 0.40, which corresponds to confidence limits between 63% and 158% of the calculated potency. If *L* is more than 0.40, repeat the test until the results from two or more tests, combined by appropriate statistical methods, meet this criterion.

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 300 per g, the test being performed on about 0.2 to 0.3 g of powder, accurately weighed.

Bacterial endotoxins ⟨85⟩—It contains not more than 10 USP Endotoxin Units per mg.

Water, *Method Ic* ⟨921⟩: not more than 10%, when prepared as a lyophilized powder.

Chromatographic purity—

Diluent—Prepare a solution of 0.05 M Tris in water, and adjust with hydrochloric acid to a pH of 7.5.

Mobile phase—Degas the *Diluent,* mix with *n*-propyl alcohol (71:29, v/v), and filter. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Resolution solution—Prepare a solution of 2.0 mg of Somatropin per mL of the *Diluent,* pass through a filter to sterilize or add sodium azide to a final concentration of 0.01%, and allow to stand at room temperature for 24 hours. [NOTE—Use within 48 hours after preparation, or store the solution in a refrigerator until ready to use.]

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Test solution—Prepare a solution of 2.0 mg of Somatropin per mL of the *Diluent* immediately before use.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 220-nm detector and a 4.6-mm × 25-cm column that contains packing L26 and is maintained at 45°. The flow rate is about 0.5 mL per minute. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the tailing factor of the somatropin peak (major peak) is between 0.9 and 1.8; and the resolution, *R,* between the somatropin peak and its adjacent peak is not less than 1.0.

Procedure—Separately inject equal volumes (about 20 µL) of the *Test solution,* record the chromatograms, and measure the area of the major peak. Calculate the percentage of impurities in Somatropin by the formula:

$$100A_I/(A_I + A_S),$$

in which A_I is the sum total of the responses of all peaks, other than the somatropin peak (major peak) and disregarding any peak due to the solvent; and A_S is the response of the somatropin peak: not more than 6.0% of total impurities is found.

Limit of high molecular weight proteins—

Phosphate buffer, Mobile phase, Diluent, Resolution solution, Test solution, and *Chromatographic system*—Proceed as directed in the *Assay.*

Procedure—Inject about 20 µL of the *Test solution*. Record the chromatogram, and measure the areas of the main peak and of the peaks eluting prior to the main peak, excluding the solvent peaks. Calculate the percentage of high molecular weight proteins in the portion of Somatropin taken by the formula:

$$100A_H/(A_H + A_M),$$

in which A_H is the sum total of the areas of the high molecular weight peaks, and A_M is the area of the monomer peak in the chromatogram of the *Test solution:* not more than 4% of high molecular weight proteins is found.

Total protein (see *Spectrophotometry and Light-Scattering* ⟨851⟩)—

Phosphate buffer—Prepare a 0.025 M solution of monobasic potassium phosphate in water, and adjust with sodium hydroxide to a pH of 7.0.

Test solution—Dissolve an accurately weighed quantity of Somatropin in *Phosphate buffer* to obtain a solution having an absorbance value between 0.5 and 1.0 at the wavelength of maximum absorbance at about 280 nm.

Procedure—Determine the absorbance of the *Test solution* using a spectrophotometric cell of path length 1-cm, at the wavelength of maximum absorbance at around 280 nm and at 320 nm, using *Phosphate buffer* as the blank. Calculate the protein content, in mg, in the portion of Somatropin taken by the formula:

$$V(A_{max} - A_{320})/0.82,$$

in which V is the volume of the *Test solution;* and A_{max} and A_{320} are the absorbance values of the *Test solution* at the wavelength of maximum absorbance and at 320 nm, respectively.

Assay—

Phosphate buffer—Prepare a 0.063 M solution of monobasic potassium phosphate in water, and adjust with sodium hydroxide to a pH of 7.0.

Mobile phase—Prepare a filtered and degassed mixture of the *Phosphate buffer* and isopropyl alcohol (97:3, v/v). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Diluent—Prepare a 0.025 M solution by dissolving monobasic potassium phosphate in water and adjusting with sodium hydroxide to a pH of 7.0.

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Resolution solution—Place one vial of USP Somatropin RS in an oven at 50° for 12 to 24 hours. Remove from the oven, and dissolve the contents of the vial in *Diluent* to obtain a solution of known concentration of about 1 mg per mL and the content of the dimer between 1% and 2%.

Standard preparation—Reconstitute a vial of USP Somatropin RS with the *Diluent* to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Dissolve an accurately weighed quantity of Somatropin in *Diluent* to obtain a solution having a concentration of about 1 mg per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 7.8-mm × 30-cm column that contains packing L33 and is maintained at ambient temperature. The flow rate is 0.6 mL per minute. Chromatograph the *Resolution solution* as directed for *Procedure:* the tailing factor of the monomer peak (major peak) is not more than 1.7; and the resolution, *R* (determined as the ratio of the valley height, between the dimer and the monomer, and the dimer peak height) is not more than 0.4.

Procedure—Separately inject equal volumes (about 20 µL) of the the *Standard preparation* and the *Assay preparation*, record the chromatograms for not less than twice the retention time of somatropin monomer peak (major peak), and measure the peak responses for the monomer. Calculate the quantity of somatropin, in µg per mg, of total protein, by the formula:

$$P(C_S / C_U)(r_U / r_S),$$

in which P is the quantity of somatropin, in µg per mg, of USP Somatropin RS; C_S and C_U are the total protein concentrations, in mg per mL, of the *Standard preparation* and the *Assay preparation,* respectively; and r_U and r_S are the peak responses of the monomer in the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Somatropin for Injection—See briefing under *Somatropin*. The proposed monograph is revised on the basis of the comments received in response to the previously published monograph (now canceled). The revisions and justifications are summarized below.

1. **Chromatographic purity**
   The requirement for a limit for any individual impurity is deleted. In the proposed monograph published in *PF* 25(4), the acceptance criteria of this test were not more than 2.0% of any individual impurity and not more than 6.0% of total impurities. It was suggested that the requirement of the individual impurity should be removed because of lack of appropriate resolution of the desamido peak from its adjacent peak and because multiple desamido peaks overlap with other impurities. Deleting the requirement for any individual impurity also is consistent with the somatropin monograph in the *European Pharmacopeia* (*EP*).
2. **Bioactivity test**
   Both Bioactivity tests (the *Cell proliferation* test and the *Rat weight-gain* test) are deleted. However, whereas the rat weight-gain test is included in the *Somatropin* monograph as a *Bioidentity* test, it is considered unnecessary for the Injection because it is not necessary to repeat an identity test for a product derived from the same drug substance.
3. **USP Reference standards**
   The requirement of USP F1 Cells for Cell Proliferation Test RS is deleted because this Reference Standard was related to the test for *Cell proliferation*, which is no longer in the new proposal.
4. **Assay**
   The word "potency" is changed to "quantity". The assay procedure is physicochemical, which measures the "quantity" of somatropin, in mg, not its bioactivity. On the other hand, the "potency" is related to its bioactivity and is measured in USP Somatropin Units (or in IU of Somatropin). However, as mentioned in the *Cell proliferation bioactivity* test under *Somatropin* the *Assay* correlates to the bioactivity, that is, potency, of somatropin.

(BNT: L. Bhattacharyya) RTS—40030-1

Add the following:

■Somatropin for Injection

» Somatropin for Injection is a sterile, lyophilized mixture of Somatropin with one or more suitable buffering and stabilizing agents. It contains not less than 89.0 percent and not more than 110.0 percent of the amount of somatropin stated on the label.

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NOTE—One mg of anhydrous Somatropin is equivalent to 3.0 USP Somatropin Units.

Packaging and storage—Preserve in tight containers, and store between 2° and 8°.

Labeling—The labeling states that the material is of recombinant DNA origin.

USP Reference standards ⟨11⟩—*USP Endotoxin RS. USP Somatropin RS.*

Identification—It meets the requirements for *Identification* test *A* under *Somatropin*.

Bacterial endotoxins ⟨85⟩—It contains not more than 20 USP Endotoxin Units per mg of somatropin.

Sterility ⟨71⟩—It meets the requirements when tested as directed for *Membrane Filtration* under *Test for Sterility of the Product to be Examined*.

Chromatographic purity—Proceed as directed in the *Chromatographic purity* test under *Somatropin:* not more than 12% of total impurities is found.

Limit of high molecular weight proteins—Proceed as directed in the test for *Limit of high molecular weight proteins* under *Somatropin,* except to use the *Assay preparation* as the *Test solution:* not more than 6% of high molecular weight proteins is found.

Assay—

Phosphate buffer, Mobile phase, Diluent, Resolution solution, Standard preparation, and *Chromatographic system*—Proceed as directed in the *Assay* under *Somatropin*.

Assay preparation—Dissolve a suitable number of vials in *Diluent* to obtain a concentration of 1 mg of somatropin per mL.

Procedure—Proceed as directed under *Somatropin*. Calculate the quantity of Somatropin, in mg, of somatropin per vial by the formula:

$$(PC_S / 1000)(V/N)(r_U / r_S),$$

in which P is the quantity of somatropin, in µg per mg, of USP Somatropin RS; C_S is the concentration, in mg per mL, of the *Standard preparation; V* is the total volume of the *Assay preparation; N* is the number of vials used to obtain the *Assay preparation;* and r_U and r_S are the peak responses of the monomer in the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Succinylcholine Chloride, *USP 26* page 1716 and page 1580 of *PF* 29(5) [Sept.–Oct. 2003]. It is proposed to replace the current test for *Chromatographic purity* with two HPLC procedures: *Test 1* uses reverse phase HPLC for the quantitation of succinylmonocholine, succinic acid, and unspecified impurities; *Test 2* uses ion chromatography for the quantitation of choline and unspecified impurities. These HPLC procedures are quantitative and selective, and provide a more accurate determination of impurities than that provided by the current thin-layer chromatographic procedure. The validation data for *Test 1* and *Test 2* were obtained using Alltima C18 and Waters X-terra MS C18 brands of L1 column, respectively. The retention times for succinylcholine chloride are about 22 minutes for *Test 1* and about 8 minutes for *Test 2*. To support *Test 2,* it is proposed to revise the *Reference standards* section to add USP Choline Chloride RS. A minor change to the note in the *Assay* is also proposed, indicating that rinsing the system with water is advisable. In addition, minor editorial style changes have been made.

(PA1: K. Russo) RTS—38599-1

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:

USP Reference standards ⟨11⟩—

■*USP Choline Chloride RS.*■2S (*USP27*)

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USP Endotoxin RS. USP Succinylcholine Chloride RS. USP Succinylmonocholine Chloride RS.

Change to read:

Chromatographic purity—

~~*Standard solution*—Transfer 18.75 mg each of choline chloride and USP Succinylmonocholine Chloride RS, accurately weighed, to a 50-mL volumetric flask, dissolve in 40 mL of methanol, dilute with methanol to volume, and mix.~~

~~*Diluted standard solution*—Transfer 4.0 mL of *Standard solution* to a 10-mL volumetric flask, dilute with methanol to volume, and mix.~~

~~*Test solution*—Prepare, immediately prior to use, a solution of Succinylcholine Chloride in methanol having a known concentration of about 50 mg per mL.~~

~~*Procedure*—Separately apply 2 µL of the *Test solution, Standard solution, and Diluted standard solution* to a suitable high-performance 10- × 10-cm thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.10-mm layer of chromatographic cellulose. Allow the spots to dry, and immediately place the plate, its coated surface toward the nearer wall, in the dry trough of a twin-trough chromatographic chamber whose other trough contains a solvent system consisting of the upper layer of a mixture of butyl alcohol, water, and 96% formic acid (65:35:15) that has been shaken and allowed to stand for 24 hours until the phases have separated. Equilibrate the chromatographic chamber for 30 minutes, and tilt the chamber to introduce the developing solvent into the trough containing the plate. Develop the chromatogram until the solvent front has moved about three-fourths of the length of the plate, remove the plate from the developing chamber, quickly and thoroughly evaporate the solvent with the aid of a current of air, and dry at 105° for 15 minutes. [NOTE—During the drying, support the plate in such a manner that only the upper and lower edges of the plate, outside the chromatographic zone, are in direct contact with any heated surface.] Spray the plate with potassium iodoplatinate TS, dry at 105° for about 2 minutes, and allow to cool to room temperature: any spots from the *Test solution* are not greater in size or intensity than the spots, occurring at the respective R_f values (approximately 0.4 for succinylmonocholine chloride, and 0.3 for choline chloride), produced by 2 µL of the *Standard solution,* corresponding to 0.75% of each compound. Estimate the size and intensities of any other spots detected by comparison with the spots produced by succinylmonocholine chloride in the *Standard solution* and in the *Diluted standard solution.* The total of any such spots detected is not more than 1.5%.~~

■TEST 1—

Buffer solution—Prepare a solution in water containing 3.85 g per liter of 1-pentanesulfonic acid, 2.9 g per liter of sodium chloride, and 1% (v/v) of 1 N sulfuric acid.

Mobile phase—Prepare a filtered and degassed mixture of acetonitrile and *Buffer solution* (5:95).

System suitability solution—Dissolve accurately weighed quantities of citric acid and succinic acid in *Mobile phase* to obtain a solution containing about 0.5 mg of each per mL .

Standard solution—Dissolve an accurately weighed quantity of USP Succinylmonocholine Chloride RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Test solution—Transfer about 100 mg of Succinylcholine Chloride, accurately weighed, to a 10-mL volumetric flask, and dissolve in and dilute with *Mobile phase* to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The chromatograph is equipped with a 214-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1 mL per minute. Samples are maintained at a temperature of about 4° during the analysis. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the relative retention times are about 0.22 for succinic acid, 0.32 for the doublet of peaks quantitated as a single component, 0.49 for succinylmonocholine chloride, and 1.0 for succinylcholine chloride; the resolution, *R,* between citric acid and succinic acid is not less than 2.9; and the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Begin integration after the edetate disodium peak (retention time is about 3.5 minutes). Calculate the percentage of each impurity in the portion of Succinylcholine Chloride taken by the formula:

$$10C(r_i / r_S)F,$$

in which C is the concentration, in mg per mL, of USP Succinylcholine Chloride RS in the *Standard solution;* r_i is the peak area for each impurity obtained from the *Test solution;* r_S is the succinylmonocholine chloride peak area obtained from the *Standard solution;* and F is the response factor (0.63 for succinic acid): not more than 0.1% of succinic acid

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is found; not more than 0.4% of the doublet of peaks quantitated as a single component is found; not more than 0.4% of succinylmonocholine chloride is found; and not more than 0.2% of any other individual impurity is found.

TEST 2 (LIMIT OF CHOLINE)—

Solution A—Prepare a solution in water containing 5% (v/v) of acetonitrile and 5% (w/v) of 0.1 M 1-hexanesulfonic acid.

Solution B—Prepare a solution of acetonitrile and water (1:1).

Mobile phase—Use variable amounts of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve an accurately weighed quantity of USP Choline Chloride RS and sodium chloride in water and dilute quantitatively, and stepwise if necessary, with water to obtain a solution containing 0.05 mg per mL and 0.5 mg per mL, respectively.

Standard stock solution—Dissolve an accurately weighed quantity of USP Choline Chloride RS in water, and dilute quantitatively, and stepwise if necessary, with water to obtain a solution containing 0.5 mg per mL.

Standard solution—Dilute 1 mL of the *Standard stock solution* with water to 50 mL.

Test solution—Transfer an accurately weighed quantity of Succinylcholine Chloride, about 50 mg, to a 25-mL flask. Dissolve in and dilute with water to volume.

Chromatographic system (see *Chromatography* ⟨621⟩)—The ion chromatograph is equipped with a cation self-regenerating suppressor, a conductivity detector at 30 µS and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The eluant flow is about 1 mL per minute and the regenerant flow is about 10 mL per minute at 50 mA output. The chromatograph is programmed as follows:

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–15	100	0	isocratic
15–16	100→0	0→100	linear gradient
16–25	0	100	isocratic
25–27	0→100	100→0	linear gradient
27–40	100	0	isocratic

Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between the sodium and choline peaks is not less than 2.0; and the relative standard deviation for replicate injections is not more than 3.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of choline in the portion of Succinylcholine Chloride taken by the formula:

$$37.5C(r_C / r_S),$$

in which C is the concentration, in mg per mL, of USP Choline Chloride RS in the *Standard solution;* and r_C and r_S are the choline peak areas obtained from the *Test solution* and *Standard solution,* respectively: not more than 0.3% of choline is found. Calculate the percentage of any other impurity present by the formula:

$$50C(r_i / r_S),$$

in which C is the concentration, in mg per mL, of USP Choline Chloride RS in the *Standard solution;* r_i is the peak area of each impurity obtained from the *Test solution;* and r_S is the choline peak area obtained from the *Standard solution:* not more than 1.5% of total impurities is found, the results for *Test 1* and *Test 2* being added.■2S (*USP27*)

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Change to read:

Assay—[NOTE—Since the *Mobile phase* employed in this procedure has a fairly high concentration of chloride ion and a low pH, it ~~may be~~

■is■2S (*USP27*)
advisable to rinse the entire system with water following the use of this *Mobile phase.*]

Mobile phase—Prepare a 1 in 10 solution of 1 N aqueous tetramethylammonium chloride in methanol. Filter this solution through a 0.45-µm membrane filter, and adjust with hydrochloric acid to a pH of about 3.0.

Standard preparation—Transfer about 88 mg of USP Succinylcholine Chloride RS, accurately weighed, to a 10-mL volumetric flask, add 4.0 mL of water, and dilute with *Mobile phase* to volume while mixing. Prepare the *Standard preparation* concurrently with the *Assay preparation.*

Assay preparation—Transfer about 88 mg of Succinylcholine Chloride, accurately weighed, to a 10-mL volumetric flask, add 4.0 mL of water, and dilute with *Mobile phase* to volume while mixing.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 214-nm detector and a 4-mm × 25-cm column that contains packing L3. The flow rate is about 0.75 mL per minute. Chromatograph five replicate injections of the *Standard preparation,* and record the peak responses as directed for *Procedure:* the tailing factor is not greater than 2.5; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph by means of a suitable microsyringe or sampling valve, record the chromatograms, and measure the responses for the major peaks. Calculate the quantity, in mg, of $C_{14}H_{30}Cl_2N_2O_4$ in the Succinylcholine Chloride taken by the formula:

$$10C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of anhydrous succinylcholine chloride in the *Standard preparation,* as determined from the concentration of USP Succinylcholine Chloride RS corrected for moisture content by a titrimetric water determination; r_U is the peak response obtained from the *Assay preparation;* and r_S is the average peak response obtained from the *Standard preparation.*

BRIEFING

Succinylcholine Chloride for Injection, *USP 26* page 1718. It is proposed to revise the test for *Chromatographic purity* to incorporate the thin-layer chromatographic procedure from the monograph for *Succinylcholine Chloride*. The current cross-reference is obsolete due to a pending revision to the *Succinylcholine Chloride* monograph.

(PA1: K. Russo) RTS—40374-1

Change to read:

Chromatographic purity—

~~*Standard solution*—Prepare as directed in the test for *Chromatographic purity* under *Succinylcholine Chloride,* using 20 mg of choline chloride and of USP Succinylmonocholine Chloride RS.~~

~~*Test solution* and *Procedure*—Proceed as directed for *Test solution* and *Procedure* in the test for *Chromatographic purity* under *Succinylcholine Chloride:* any spots from the *Test solution* are not greater in size or intensity than the spots, occurring at the respective R_x values (approximately 0.6 for succinylmonocholine chloride and 0.5 for choline chloride), produced by 5 µL of the *Standard solution,* corresponding to 1.0% of each compound. Estimate the size and intensities of any other spots detected by comparison with the spot produced by succinylmonocholine chloride in the *Standard solution.* The total of any such spots detected is not more than 2.0%.~~

■*Standard solution*—Transfer 20 mg each of choline chloride and USP Succinylmonocholine Chloride RS, accurately weighed, to a 50-mL volumetric flask, dissolve in 40 mL of methanol, dilute with methanol to volume, and mix.

Test solution—Prepare, immediately prior to use, a solution of Succinylcholine Chloride in methanol having a concentration of about 50 mg per mL.

Procedure—Separately apply 2 µL of the *Test solution* and 5 µL of the *Standard solution* to a suitable high-performance 10- × 10-cm thin-layer chromatographic plate (see *Chromatography* ⟨621⟩) coated with a 0.10-mm layer of chromatographic cellulose. Allow the spots to dry, and immediately place the plate, its coated surface toward the nearer wall, in the dry trough of a twin-trough chromatographic chamber whose other trough contains a solvent system consisting of the upper layer of a mixture of butyl alcohol, water, and 96% formic acid (65:35:15) that has been shaken and allowed to stand for 24 hours until the phases have separated. Equilibrate the chromatographic chamber for 30 minutes, and tilt the chamber to introduce the developing solvent into the trough containing the plate. Develop the chromatogram until the solvent front has moved about three-fourths of the length of the plate, remove the plate from the developing chamber, quickly and thoroughly evaporate the solvent with the aid of a current of air, and dry at 105° for 15 minutes. [NOTE—During the dry-

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ing, support the plate in such a manner that only the upper and lower edges of the plate, outside the chromatographic zone, are in direct contact with any heated surface.] Spray the plate with potassium iodoplatinate TS, dry at 105° for about 2 minutes, and allow to cool to room temperature: any spots from the *Test solution* are not greater in size or intensity than the spots, occurring at the respective R_F values (approximately 0.6 for succinylmonocholine chloride, and 0.5 for choline chloride), produced by 5 µL of the *Standard solution,* corresponding to 0.8% of each compound. Estimate the size and intensities of any other spots detected by comparison with the spot produced by succinylmonocholine chloride in the *Standard solution*. The total of any such spots detected is not more than 2.0%.■2S (*USP27*)

BRIEFING

Sufentanil Citrate, *USP 26* page 1720—See briefing under *Alfentanil Hydrochloride*.

(PA2: C. Anthony; PSD: C. Okeke) RTS—40357-1

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Sufentanil Citrate RS.

Add the following:

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

BRIEFING

Sulfadiazine Sodium, *USP 26* page 1731—See briefing under *Acyclovir*.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-15

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Sulfadiazine RS.

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Add the following:

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

BRIEFING

Sulfamethizole Oral Suspension, *USP 26* page 1736—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-6

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Sulfamethoxazole, *USP 26* page 1737—See briefing under *Acyclovir*.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-16

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Add the following:

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

BRIEFING

Sulfamethoxazole Oral Suspension, *USP 26* page 1737—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-7

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Sulfisoxazole Acetyl Oral Suspension, *USP 26* page 1746—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-9

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Sulfamethoxazole and Trimethoprim Oral Suspension, *USP 26* page 1739 and page 670 of *PF* 29(3) [May–June 2003]—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-8

Delete the following:

■~~Pharmacy Equivalent Name: Co-trimoxazole Oral Suspension~~■1S (*USP27*)

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Thiabendazole Oral Suspension, *USP 26* page 1811—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-10

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Thiabendazole Tablets, *USP 26* page 1811. It is proposed to change the title of this monograph to *Thiabendazole Chewable Tablets.* See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40432-1

Thiabendazole Tablets

(Current title—not to change until February 1, 2007)
Monograph title change—to become official February 1, 2007
(see Official Title Changes on the first page of In-Process Revision):
***See* Thiabendazole Chewable Tablets**

BRIEFING

Thiabendazole Chewable Tablets—See briefing under *Alumina, Magnesia, and Calcium Carbonate Tablets.*

(NL: C. Barnstein; W. Paul) RTS—40432-1

Add the following:

■Thiabendazole Chewable Tablets

(Monograph under this new title—to become official February 1, 2007)
(Current monograph title is Thiabendazole Tablets)

» Thiabendazole Chewable Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amount of $C_{10}H_7N_3S$.

Packaging and storage—Preserve in tight containers.

Labeling—Label the Chewable Tablets to indicate that they are to be chewed before swallowing.

USP Reference standards ⟨11⟩—*USP Thiabendazole RS.*

Identification—

A: Triturate a quantity of powdered Chewable Tablets, equivalent to about 0.5 g of thiabendazole, with about 20 mL of water, and filter. Wash the residue with 20 mL of water, discard the washing, dissolve the residue in 30 mL of 0.1 N hydrochloric acid, and filter. Collect the filtrate in a separator, render it alkaline with 1 N sodium hydroxide, and extract with 10 mL of carbon disulfide. Filter the carbon disulfide layer through a dry filter, collecting the filtrate in an evaporating dish. Evaporate the solvent with the aid of gentle heat and a stream of nitrogen. [*Caution—Do not overheat the residue*.] The residue so obtained responds to *Identification* test *A* under *Thiabendazole*.

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

Uniformity of dosage units ⟨905⟩: meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Standard preparation—Dissolve an accurately weighed quantity of USP Thiabendazole RS in 0.1 N hydrochloric acid, and dilute quantitatively and stepwise with 0.1 N hydrochloric acid to obtain a solution having a known concentration of about 5 µg per mL.

Test preparation—Transfer 1 Chewable Tablet to a 1000-mL volumetric flask, add about 75 mL of 0.1 N hydrochloric acid, and heat on a steam bath for about 1 hour. Cool to room temperature, dilute with 0.1 N hydrochloric acid to volume, mix, and filter a portion of the solution, discarding the first 20 mL of the filtrate. Pipet 5 mL of the filtrate into a 500-mL volumetric flask, dilute with 0.1 N hydrochloric acid to volume, and mix.

Procedure—Concomitantly determine the absorbances of the *Standard preparation* and the *Test preparation* at the wavelength of maximum absorbance at about 302 nm, with

a suitable spectrophotometer, using 0.1 N hydrochloric acid as the blank. Calculate the quantity, in mg, of $C_{10}H_7N_3S$ in the Chewable Tablet taken by the formula:

$$(TC/D)(A_U/A_S),$$

in which T is the labeled quantity, in mg, of thiabendazole in the Chewable Tablet; C is the concentration, in µg per mL, of USP Thiabendazole RS in the *Standard preparation; D* is the concentration, in µg per mL, of thiabendazole in the *Test preparation,* based upon the labeled quantity per Chewable Tablet and the extent of dilution; and A_U and A_S are the absorbances of the *Test preparation* and the *Standard preparation,* respectively.

Assay—

Standard preparation and *Chromatographic system*—Prepare as directed in the *Assay* under *Thiabendazole Oral Suspension*.

pH 3.5 Phosphate buffer—Dissolve 13.8 g of monobasic sodium phosphate in water to obtain 2000 mL of solution. Adjust this solution with phosphoric acid to a pH of 3.5 ± 0.05.

Mobile phase—Prepare a filtered and degassed mixture of *pH 3.5 Phosphate buffer* and methanol (54:46). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Assay preparation—Weigh and finely powder not fewer than 20 Chewable Tablets. Transfer an accurately weighed portion of the powder, equivalent to about 200 mg of thiabendazole, to a 1000-mL volumetric flask, add 100 mL of 0.1 N hydrochloric acid, mix, and warm the solution for a minimum of 30 minutes. Allow to cool to room temperature, dilute with water to volume, mix, and filter, discarding the first 20 mL of the filtrate.

Procedure—Proceed as directed for *Procedure* in the *Assay* under *Thiabendazole Oral Suspension*. Calculate the quantity, in mg, of $C_{10}H_7N_3S$ in the portion of Chewable Tablets taken by the formula:

$$1000C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Thiabendazole RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

(Official February 1, 2007)

BRIEFING

Thioridazine Oral Suspension, *USP 26* page 1823—See briefing under *Carbamazepine Oral Suspension*.

(PA3: S. Salado) RTS—40408-16

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

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BRIEFING

Thiothixene Hydrochloride, *USP 26* page 1828—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-39

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Thiothixene RS. USP (E)-Thiothixene RS.

Add the following:

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

BRIEFING

Thiothixene Hydrochloride Oral Solution, *USP 26* page 1829—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-17

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Trifluoperazine Hydrochloride, *USP 26* page 1880—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-40

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Trifluoperazine Hydrochloride RS.

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Triflupromazine Hydrochloride RS.

Add the following:

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

BRIEFING

Trifluprom azine Hydrochloride, *USP 26* page 1884—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-41

Change to read:

Packaging and storage—Preserve in well-closed, light-resistant glass containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

BRIEFING

Triflupromazine Oral Suspension, *USP 26* page 1883—See briefing under *Carbamazepine Oral Suspension.*

(PA3: S. Salado) RTS—40408-18

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SNGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

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BRIEFING

Trimethoprim, *USP 26* page 1893 and page 1080 of *PF* 29(4) [July–Aug. 2003]—See briefing under *Acyclovir*. In the proposed section for *Other requirements*, the test for *Bacterial endotoxins* is not specified; instead, it is proposed to specify use of the *Pyrogen Test* ⟨151⟩.

(PA7b: B. Davani) RTS—40237-17

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

Identification—

A: *Infrared Absorption* ⟨197S⟩—
Solution: 1 in 100.
Medium: chloroform.

B: Transfer about 100 mg of it, accurately weighed, to a 100-mL volumetric flask, and dissolve in 25 mL of alcohol. Dilute quantitatively and stepwise with sodium hydroxide solution (1 in 250) to obtain a 1 in 50,000 solution: the UV absorption spectrum of this solution exhibits maxima and minima only at the same wavelengths as that of a similar solution of USP Trimethoprim RS, concomitantly measured; and the respective absorptivities, calculated on the dried basis

■for the test sample only,■1S (*USP27*)
at the wavelength of maximum absorbance at about 287 nm do not differ by more than 3.0%.

Add the following:

■**Other requirements—**Where the label states that Trimethoprim is sterile, it meets the requirements under *Sterility* ⟨71⟩. Where the label states that it is intended for use in preparing injectable dosage forms or must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Pyrogen* under *Sulfamethoxazole and Trimethoprim Injection*.■2S (*USP27*)

BRIEFING

Trimethoprim Sulfate, *USP 26* page 1894—See briefing under *Acyclovir*. In the proposed section for *Other requirements*, the test for *Bacterial endotoxins* is not specified; instead, it is proposed to specify use of the *Pyrogen Test* ⟨151⟩ Also, in the section *USP Reference standards* ⟨11⟩, it is proposed to delete USP 3-Anilino-2-(3,4,5-trimethoxy-benzyl)-acrylonitrile RS because that Reference Standard is not needed for this monograph.

(PA7b: B. Davani; PSD: C. Okeke) RTS—40237-18

Change to read:

Packaging and storage—Preserve in well-closed containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—*USP Trimethoprim RS*. ~~USP 3-Anilino-2-(3,4,5-trimethoxy-benzyl)acrylonitrile RS.~~

■■2S (*USP27*)

Add the following:

■**Other requirements—**Where the label states that Trimethoprim Sulfate is sterile, it meets the requirements under *Sterility* ⟨71⟩. Where the label states that it is intended for use in preparing injectable dosage forms or must be subjected to further processing during the preparation of injectable dosage forms, it meets the requirements for *Pyrogen* under *Sulfamethoxazole and Trimethoprim Injection*.■2S (*USP27*)

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BRIEFING

Trisulfapyrimidines Oral Suspension, *USP 26* page 1901—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-11

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SUSPENSION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SUSPENSION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Tubocurarine Chloride, *USP 26* page 1907—See briefing under *Amitriptyline Hydrochloride.*

(PA3: S. Salado; PSD: C. Okeke) RTS—40364-42

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Tubocurarine Chloride RS.

Add the following:

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

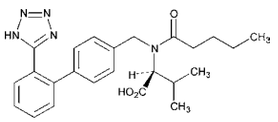
BRIEFING

Valsartan, page 1590 of *PF* 29(5) [Sept.–Oct., 2003]. This new monograph is presented again with additional changes. Detector wavelengths are changed in *Related compounds Test 1* and in the *Assay.* The *Standard solution* in *Test 1* is also corrected.

(PA5: A. Wilk) RTS—40405-1

Add the following:

■Valsartan



$C_{24}H_{29}N_5O_3$ ~~435.53~~ 435.52

L-Valine, *N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl)[1,1′-biphenyl]-4-yl]methyl].

N-[*p*-(*o*-1*H*-Tetrazol-5-yl-phenyl)benzyl]-*N*-valeryl-L-valine [*137862-53-4*].

» Valsartan contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{29}N_5O_3$, calculated on the anhydrous basis.

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Packaging and storage—Preserve in ~~well-closed containers.~~ tight containers, and store at 25°; excursions are permitted between 15° and 30°. Protect from moisture and heat.

USP Reference standards ⟨11⟩—*USP Valsartan RS. USP Valsartan Related Compound A RS. USP Valsartan Related Compound B RS. USP Valsartan Related Compound C RS.*

Identification—

A: *Infrared Absorption* ⟨197M⟩.

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

Absorbance: not more than ~~0.070~~ 0.07, determined at 420 nm, in a 4-cm cell, on a solution prepared by dissolving 1 g in 20 mL of methanol.

~~**Specific rotation** ⟨781S⟩: between −64° and −69° at 20°.~~

~~*Test solution:* 10 mg per mL, in methanol.~~

Water, *Method I* ⟨921⟩: not more than 2.0%.

Residue on ignition ⟨281⟩: not more than 0.1%.

Heavy metals, *Method II* ⟨231⟩: 0.001%.

Related compounds—

TEST 1 (LIMIT OF VALSARTAN RELATED COMPOUND A)—

~~*0.07 M Phosphate buffer solution*—Dissolve 10.99 g of dibasic sodium phosphate and 3.81 g of monobasic potassium phosphate in water, dilute with water to 1000 mL, and mix.~~

Mobile phase—Prepare a ~~filtered and degassed~~ mixture of ~~*0.07 M Phosphate buffer solution* and isopropyl alcohol (98:2).~~ *n*-hexane, 2-propanol, and trifluoroacetic acid (85:15:0.1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—~~Pipet 5.0 mL of *System suitability solution* into a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix. Dissolve an accurately weighed quantity of USP Valsartan Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.003 mg of valsartan related compound A per mL.~~ Transfer about 5 mg of USP Valsartan Related Compound A RS, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Standard solution—Transfer 1.0 mL of *Standard stock solution* into a 10-mL volumetric flask, dilute with *Mobile phase,* and mix. ~~Transfer 1.0 mL of this solution into a 10-mL volumetric flask, dilute with *Mobile phase,* and mix.~~

System suitability solution—~~Transfer about 30 mg of USP Valsartan Related Compound A, accurately weighed, to a 100-mL volumetric flask, and dissolve in and dilute with *Mobile phase* to volume. Pipet 5.0 mL of this solution into a 50-mL volumetric flask, and dilute with *Mobile phase* to volume (*Solution 1*). Transfer about 15 mg of USP Valsartan RS, accurately weighed, to a 100-mL volumetric flask, and dissolve in *Mobile phase*. Add, by pipetting, 10.0 mL of *Solution 1* to the same flask, dilute with *Mobile phase* to volume, and mix. Dissolve accurately weighed quantities of USP Valsartan RS and USP Valsartan Related Compound A RS in *Mobile phase,* serially diluting, if necessary, to obtain a solution having a known concentration of about 0.15 mg of valsartan per mL and about 0.003 mg of valsartan related compound A per mL.~~ Transfer about 1 mg of Valsartan, accurately weighed, to a ~~20-mL~~ 25-mL volumetric flask, add 10 mL of the *Standard stock solution,* and dissolve in and dilute with *Mobile phase* to volume.

Test solution—~~Transfer about 100 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 5.0 mL of this solution into a 25-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~ Transfer about 50

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mg of Valsartan, accurately weighed, to a 50-mL volumetric flask, add about 40 mL of *Mobile phase,* and sonicate for 5 minutes. Dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a ~~227-nm 220-nm~~ 230-nm detector and a ~~4.0-mm × 10-cm~~ 4.6-mm × 25-cm column that contains 5-µm packing ~~L41~~ L40. The flow rate is about 0.8 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are 0.60 for valsartan related compound A and 1.0 for valsartan; the ratio of the height between the baseline and the lowest point between the valsartan and valsartan related compound A peaks to the height of the valsartan related compound A peak is not more than 0.4. and~~ the resolution, *R,* between valsartan related compound A and valsartan is not less than 2.0. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation, determined from the valsartan related compound A peaks, for replicate injections is not more than ~~15.0%~~ 5%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the ~~heights~~ areas for the major peaks. Calculate the percentage of valsartan related compound A in the portion of Valsartan taken by the formula:

~~$100(r_U/r_S),$~~

~~in which r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than 1.5% is found.~~

$$100(C_S/C_U)(r_U/r_S),$$

in which C_S is the concentration, in mg per mL, of USP Valsartan Related Compound A RS in the *Standard solution;* C_U is the concentration, in mg per mL, of valsartan in the *Test solution;* and r_U and r_S are the peak responses for valsartan related compound A obtained from the *Test solution* and *Standard solution,* respectively: not more than ~~1.5%~~ 1.0% is found.

TEST 2 (LIMIT OF VALSARTAN RELATED COMPOUND B, VALSARTAN RELATED COMPOUND C, AND OTHER RELATED COMPOUNDS)—

~~*Diluent* and~~ *Mobile phase*—Proceed as directed in the *Assay.*

~~*Standard stock solution A*—Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase* to obtain a solution having a known concentration of about 5 mg per mL.~~

~~*Standard stock solution B*—Dissolve an accurately weighed quantity of USP Valsartan Related Compound B RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.05 mg per mL.~~

~~*Standard stock solution C*—Dissolve an accurately weighed quantity of USP Valsartan Related Compound C RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.025 mg per mL.~~

Resolution solution—~~Pipet 10.0 mL of *Standard stock solution A,* 5.0 mL of *Standard stock solution B,* and 2.0 mL of *Standard stock solution C* into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.~~ Dissolve accurately weighed quantities of USP Valsartan RS, USP Valsartan Related Compound B RS, and USP Valsartan Related Compound C RS in *Mobile phase,* serially diluting if necessary, to obtain a solution having known concentrations of about ~~0.5 mg~~ 0.001 mg of valsartan per mL, ~~0.0025 mg~~ 0.001 mg of valsartan related compound B per mL, and ~~0.0005 mg~~ 0.001 mg of valsartan related compound C per mL.

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Standard solution—~~Dilute an accurately measured volume of *Standard stock solution A* quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about 0.0005 mg per mL.~~ Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about ~~0.0005 mg~~ 0.001 mg of valsartan per mL.

Test solution—Transfer about 50 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Prepare as directed in the *Assay,* except to use a 225-nm detector. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* ~~the relative retention times are 0.73 for valsartan related compound B, 1.0 for valsartan, and 3.8 for valsartan related compound C;~~ the resolution, *R,* between valsartan related compound B and valsartan is not less than 1.8; and the relative standard deviation, determined from the valsartan related compound B peaks, for replicate injections is not more than ~~5.0%~~ 10.0%, and the relative standard deviation, determined from the valsartan peaks, for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Resolution solution, Standard solution,* and *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of ~~each impurity~~ valsartan related compound B and valsartan related compound C in the portion of Valsartan taken by the formula:

~~$100(Dr_i/r_u)$,~~

~~in which *D* is the factor due to the extent of dilution and is equal to 2.5 for valsartan related compound B, 0.5 for valsartan related compound C, and 0.05 for all other impurities; r_i is the peak response for each impurity obtained from the *Test solution;* and r_u is the peak response for valsartan related compound B or valsartan related compound C obtained from the *Resolution solution* or the valsartan peak response obtained from the *Standard solution,* as appropriate:~~

$$100(C_S/C_u)(r_i/r_S),$$

in which C_S is the concentration, in mg per mL, of the appropriate USP Valsartan Related Compound RS in the *Resolution solution;* C_u is the concentration, in mg per mL, of valsartan in the *Test solution;* r_i is the peak response for the impurity obtained from the *Test solution;* and r_S is the peak response for the appropriate valsartan related compound obtained from the *Resolution solution.* Calculate the percentage of each other impurity in the portion of Valsartan taken by the formula:

$$100(C_S/C_u)(r_i/r_S),$$

in which C_S is the concentration, in mg per mL, of USP Valsartan RS in the *Standard solution;* r_S is the peak response for valsartan obtained from the *Standard solution;* and the other terms are as defined above: not more than ~~0.5%~~ 0.2% of valsartan related compound B is found; not more than 0.1% of valsartan related compound C is found; not more than 0.1% of any other individual impurity, excluding the valsartan related compound A, is found; ~~and not more than 0.5% of total impurities is found.~~ and not more than 0.3% of total impurities, excluding valsartan related compound A, is found.

Assay—

~~*Diluent*—Prepare a mixture of acetonitrile and water (1:1).~~

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Mobile phase—Prepare a filtered and degassed mixture of water, acetonitrile, and glacial acetic acid (500:500:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP Valsartan RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having a known concentration of about ~~0.05 mg~~ 0.5 mg per mL.

Assay preparation—Transfer about 50 mg of Valsartan, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix. Pipet 10.0 mL of this solution into a 100-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system—The liquid chromatograph is equipped with a ~~230-nm 248-nm~~ 273-nm detector and a 3.0-mm × 12.5-cm column that contains 5-µm packing L1. The flow rate is about 0.4 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* ~~the tailing factor is between 0.8 and 1.5; and~~ the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the quantity, in mg, of $C_{24}H_{29}N_5O_3$ in the portion of Valsartan taken by the formula:

~~$1000C(r_U/r_S)$,~~

$$100C(r_U/r_S),$$

in which C is the concentration, in mg per mL, of USP Valsartan RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively. ■2S (*USP27*)

BRIEFING

Valsartan and Hydrochlorothiazide Tablets, page 1954 of *PF* 29(5) [Sept.–Oct. 2003]. This monograph is presented again with additional changes. It is proposed to revise the test for *Related compounds* to remove valsartan related compound B from the impurity limit exclusion.

(PA5: A. Wilk) RTS—40406-1

Add the following:

■Valsartan and Hydrochlorothiazide Tablets

» Valsartan and Hydrochlorothiazide Tablets contain not less than 90.0 percent and not more than 110.0 percent of the labeled amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

Packaging and storage—Preserve in ~~well-closed containers.~~ tight containers, and store at 25°; excursions are permitted between 15° and 30°. Protect from moisture and heat.

USP Reference standards ⟨11⟩—~~*USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS.*~~ *USP Benzothiadiazine Related Compound A RS. USP Hydrochlorothiazide RS. USP Valsartan RS. USP Valsartan Related Compound B RS.*

Identification—

A: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—

Test solution—To a centrifuge tube transfer an amount of ground Tablets, equivalent in weight to a single Tablet, add 2.0 mL of acetone, sonicate for 15 minutes, and centrifuge.

Application volume: 2 µL.

Developing solvent system: a mixture of ethyl acetate, dehydrated alcohol, and a solution (25 in 100) of ammonium hydroxide (8:2:1).

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Procedure—Proceed as directed in the chapter, except to develop the plate in a paper-lined chromatographic chamber equilibrated with *Developing solvent system* for about 15 minutes prior to use. Allow the chromatogram to develop until the solvent front has moved at least 7 cm. After removing the plate and marking the solvent front, dry the plate under a current of warm air until it is completely dry. The R_F values of the principal spots obtained from the *Test solution* correspond to those obtained from the Standard solution.

B: The retention times of the major peaks in the chromatogram of the *Assay preparation* correspond to those in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

Dissolution ⟨711⟩—

Medium: pH 6.8 phosphate buffer; 1000 mL.

Apparatus 2: 50 rpm.

Time: ~~45~~ 30 minutes.

Procedure—Determine the amounts of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved by employing UV absorption at the wavelengths of maximum absorbance at about 250 nm for valsartan ~~(corrected for interference from hydrochlorothiazide on the basis of the absorbances of hydrochlorothiazide at 250 and 272 nm)~~ and at about 272 nm for hydrochlorothiazide on filtered portions of the solution under test, ~~suitably diluted with *Dissolution Medium,* in comparison with a Standard solution having known concentrations of USP Valsartan RS and USP Hydrochlorothiazide RS in the same *Medium*~~ diluted with *Medium* if necessary. Calculate the quantity of $C_{24}H_{29}N_5O_3$ dissolved, in mg, by the formula:

$$1000D\left(\frac{A_{\text{obs}250}a_{\text{H}272}-A_{\text{obs}272}a_{\text{H}250}}{a_{\text{V}250}a_{\text{H}272}-a_{\text{V}272}a_{\text{H}250}}\right),$$

in which D is the sample dilution factor if used; $A_{\text{obs}250}$ is the observed absorbance of the sample solution at 250 nm; $A_{\text{obs}272}$ is the observed absorbance of the sample solution at 272 nm; $a_{\text{V}250}$ is the absorptivity of valsartan at 250 nm; $a_{\text{V}272}$ is the absorptivity of valsartan at 272 nm; $a_{\text{H}250}$ is the absorptivity of hydrochlorothiazide at 250 nm; and $a_{\text{H}272}$ is the absorptivity of hydrochlorothiazide at 272 nm. The absorptivities, *a,* are determined from separate Standard solutions of USP Valsartan RS and USP Hydrochlorothiazide RS in the *Medium* having known concentration and expressed in units as defined by *Spectrophotometry and Light-Scattering* ⟨851⟩. Calculate the quantity of $C_7H_8ClN_3O_4S_2$ dissolved, in mg, by the formula:

$$1000D\left(\frac{A_{\text{obs}272}a_{\text{V}250}-A_{\text{obs}250}a_{\text{V}272}}{a_{\text{V}250}a_{\text{H}272}-a_{\text{V}272}a_{\text{H}250}}\right),$$

in which the terms are as defined above.

Tolerances—Not less than ~~75%~~ 80% (Q) of the labeled amounts of $C_{24}H_{29}N_5O_3$ and $C_7H_8ClN_3O_4S_2$ is dissolved in ~~45~~ 30 minutes.

Uniformity of dosage units ⟨905⟩: meet the requirements.

PROCEDURE FOR CONTENT UNIFORMITY—

Diluent, Solution A, Solution B, Mobile phase, and *Chromatographic system*—Prepare as directed in the *Assay.*

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

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Test solution—Place 1 Tablet in a 200-mL volumetric flask, add 5 mL of water, and allow to stand for 5 minutes. Add about 100 mL of *Diluent,* and sonicate for 15 minutes. Dilute with *Diluent* to volume, mix, and centrifuge a portion of this solution at about 3000 rpm. Quantitatively dilute a volume of the clear supernatant with *Diluent* to obtain a solution having a concentration of about 0.2 mg of valsartan per mL.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the quantities, in mg, of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the Tablet taken by the formula:

$$(LC_S / C_U)(r_U / r_S),$$

in which L is the labeled quantity, in mg, of the relevant analyte in the Tablet; C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard solution;* C_U is the concentration, in mg per mL, of the corresponding analyte in the *Test solution,* based on the labeled quantity per Tablet and the extent of dilution; and r_U and r_S are the peak responses obtained from the *Test solution* and the *Standard solution,* respectively.

Related compounds—

Diluent, Solution A, Solution B, and *Mobile phase*—Prepare as directed in the *Assay.*

Standard stock solution—Dissolve accurately weighed quantities of ~~USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS,~~ USP Benzothiadiazine Related Compound A RS, USP Hydrochlorothiazide RS, USP Valsartan RS, and USP Valsartan Related Compound B RS in *Diluent* to obtain a solution having known concentrations of about 0.03 mg per mL, 0.06 mg per mL, 0.08 mg per mL, and 0.2 mg per mL, respectively.

Resolution solution—Dilute 5.0 mL of *Standard stock solution* with *Diluent* to 100.0 mL, and mix.

Standard solution—Dilute 10.0 mL of *Resolution solution* with *Diluent* to 100.0 mL, and mix.

Test solution—Use the *Assay preparation* as specified.

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between valsartan related compound B and valsartan, and between ~~4-amino-6-chloro-1,3-benzenedisulfonamide~~ benzothiadiazine related compound A and hydrochlorothiazide is not less than 1.4. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation, determined from the valsartan and hydrochlorothiazide peaks, for replicate injections is not more than 10.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks, disregarding the peak, if any, with a retention time of about 22 minutes. Calculate the quantity, in mg, of each impurity in the portion of Tablets taken by the formula:

$$2000C(r_U / r_S),$$

in which C is the concentration, in mg per mL, of ~~USP Valsartan Related Compound B RS or USP 4-Amino-6-chloro-1,3-benzenedisulfonamide RS,~~ USP Benzothiadiazine Related Compound A RS, or the relevant USP Reference Standard (when determining the quantity of other impurities) in the *Standard solution;* and r_U and r_S are the corresponding peak responses obtained from the *Test solution* and the *Standard solution,* respectively: not more than ~~0.5%~~ 1.0% ~~each of valsartan related compound B and~~ of ~~4-amino-6-chloro-1,3-benzenedisulfonamide~~ benzothiadiazine related compound A is found; not more than 0.2% of any other impurity,

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excluding valsartan related compound A ~~and valsartan related compound B~~, is found; and not more than ~~0.8%~~ 1.3% of total impurities, excluding valsartan related compound A ~~and valsartan related compound B~~, is found. [NOTE—Valsartan related compound A is the enantiomer of valsartan and coelutes with valsartan in this test.]

Assay—

Diluent—Prepare a mixture of acetonitrile and water (1:1).

Solution A—Prepare a filtered and degassed mixture of water, acetonitrile, and trifluoroacetic acid (90:10:0.1).

Solution B—Prepare a filtered and degassed mixture of acetonitrile, water, and trifluoroacetic acid (90:10:0.1).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system.* Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Transfer about 12.5 mg of USP Hydrochlorothiazide RS, accurately weighed, to a 200-mL volumetric flask. Add about 12.5*J* mg of USP Valsartan RS, accurately weighed, *J* being the ratio of the labeled amount, in mg, of valsartan to the labeled amount, in mg, of hydrochlorothiazide per Tablet. Add about 100 mL of *Diluent,* sonicate for 15 minutes, dilute with *Diluent* to volume, and mix. Transfer 25.0 mL of this solution to a 50-mL volumetric flask, dilute with *Diluent* to volume, and mix. Quantitatively dilute a volume of this solution with *Diluent* to obtain a solution having a known concentration of about 0.2 mg of USP Valsartan RS per mL.

Assay preparation—Transfer a number of Tablets, equivalent to about 62.5 mg of hydrochlorothiazide, to a 250-mL volumetric flask. Add 5 mL of water, and allow to stand for 5 minutes. Then add about 100 mL of *Diluent,* sonicate for 15 minutes, and shake for 30 minutes. Dilute with *Diluent* to volume, mix, and centrifuge a portion of this solution at 3000 rpm. Dilute 25.0 mL of the clear supernatant with *Diluent* to 200.0 mL, and mix *(Solution 1).* [NOTE—Retain a portion of *Solution 1* to use as the *Test solution* in the test for *Related compounds*.] Dilute an accurately measured volume of *Solution 1* with *Diluent* to obtain a solution containing about 0.2 mg of valsartan per mL.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 265-nm detector and a 3.0-mm × 12.5-cm column that contains 5-µm packing L1. The flow rate is about 0.4 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0–25	90→10	10→90	linear gradient
25–27	10→90	90→10	linear gradient
27–40	90	10	isocratic

Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 2.0%.

Procedure—Separately inject equal volumes (about 10 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Separately calculate the quantities, in mg, of valsartan ($C_{24}H_{29}N_5O_3$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken by the formula:

$$(LC_S / C_U)(r_U / r_S),$$

in which L is the labeled quantity, in mg, of the relevant analyte in each Tablet; C_S is the concentration, in mg per mL, of the appropriate USP Reference Standard in the *Standard preparation;* C_U is the concentration, in mg per mL, of the corresponding analyte in the *Assay preparation,* based on the labeled quantity per Tablet and the extent of dilution;

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and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.■2S (*USP27*)

BRIEFING

Vasopressin, *USP 26* page 1923—See briefing under *Acepromazine Maleate*.

(BNT: I. DeVeau) RTS—40270-17

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Vasopressin RS.

Add the following:

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

BRIEFING

Vitamin A, *USP 26* page 1933. Because USP Vitamin A RS is now available in ampuls rather than soft gel capsules, it is proposed to replace the word "capsule" with "ampul" in the *Thin-Layer Chromatographic Identification Test*. In addition, the *Identification* test has been restyled to conform to current USP editorial style. In the absence of any significant adverse comment, it is proposed to implement this revision via the *Second Interim Revision Announcement* pertaining to *USP 27–NF 22,* with an official date of April 1, 2004.

(DSN: L. Evans) RTS—40298-1

Change to read:

Identification—

A: To 1 mL of a chloroform solution of it containing the equivalent of approximately 6 µg of retinol, add 10 mL of antimony trichloride TS: a transient blue color appears at once.

B: *Thin-Layer Chromatographic Identification Test* ⟨201⟩—*Test solution*—

FOR LIQUID FORM OF VITAMIN A—Dissolve a volume equivalent to about 15,000 USP Units in chloroform to obtain 10 mL of solution.

FOR SOLID FORM OF VITAMIN A—Weigh a quantity equivalent to about 15,000 USP Units, place in a separator, add 75 mL of water, shake vigorously for 1 minute, extract with 10 mL of chloroform by shaking for 1 minute, and centrifuge to clarify the chloroform extract.

Standard solution—Dissolve the contents of 1 ~~capsule~~ •ampul•2 of USP Vitamin A RS in chloroform to obtain 25.0 mL.

Developing solvent system: a mixture of cyclohexane and ether (4:1).

Procedure—Apply at the starting point of the chromatogram 0.015 mL of the *Standard solution* and 0.01 mL of the *Test solution,* and proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Allow the solvent front to move a distance of 10 cm, remove the plate, and air dry. Spray with phosphomolybdic acid TS: the blue-green spot formed is indicative of the presence of retinol. The approximate R_F values of the predominant spots, corresponding to the different forms of retinol, are 0.1 for the alcohol form, 0.45 for the acetate, and 0.7 for the palmitate.

BRIEFING

Xylazine, *USP 26* page 1942 and page 3002 of the *First Supplement*—See briefing under *Acepromazine Maleate*.

(VET: I. DeVeau; PSD: C. Okeke) RTS—40270-18

Change to read:

Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

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Change to read:
Labeling—Where it is intended for veterinary use only, the label so states.

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

Change to read:
USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Xylazine RS.

Add the following:

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

BRIEFING

Xylazine Hydrochloride, *USP 26* page 1944—See briefing under *Acepromazine Maleate*.

(VET: I. DeVeau; PSD: C. Okeke) RTS—40270-19

Change to read:
Packaging and storage—Preserve in tight containers.

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Change to read:
Labeling—Where it is intended for veterinary use only, the label so states.

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

Change to read:
USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Xylazine Hydrochloride RS.

Add the following:

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

BRIEFING

Yohimbine Hydrochloride, *USP 26* page 1947 and page 3003 of the *First Supplement*—See briefing under *Acepromazine Maleate.*

(VET: I. DeVeau) RTS—40270-20

Change to read:
Labeling—Where it is intended for veterinary use only, it is so labeled.

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

Change to read:
USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Yohimbine Hydrochloride RS.

Add the following:

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

BRIEFING

Zidovudine, *USP 26* page 1950—See briefing under *Acyclovir*.

(PA7b: B. Davani) RTS—40237-19

Change to read:

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

■Store at 25°, excursions permitted between 15° and 30°.■2S (*USP27*)

Add the following:

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

Change to read:

USP Reference standards ⟨11⟩—

■*USP Endotoxin RS.*■2S (*USP27*)
USP Zidovudine RS. USP Zidovudine Related Compound B RS. USP Zidovudine Related Compound C RS.

Add the following:

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

BRIEFING

Zidovudine Oral Solution, *USP 26* page 1952—See briefing under *Acyclovir Oral Suspension*.

(PA7b: B. Davani) RTS—40399-12

Add the following:

■**Uniformity of dosage units** ⟨905⟩—

FOR ORAL SOLUTION PACKAGED IN SINGLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

Add the following:

■**Deliverable volume** ⟨698⟩—

FOR ORAL SOLUTION PACKAGED IN MULTIPLE-UNIT CONTAINERS: meets the requirements.■2S (*USP27*)

BRIEFING

Zileuton, page 3003 of the *First Supplement* and page 447 of *PF* 29(2) [Mar.–Apr. 2003]. It is proposed to add a *Note* to the procedures in the test for *Chromatographic purity* and in the *Assay* specifying that immediately after preparation and during analysis, solutions containing Zileuton should be stored at or below 5°. It is known that Zileuton degrades in solution at room temperature; refrigeration of solutions is necessary to ensure the accurate determination of impurity levels.

(PA1: K. Russo) RTS—39706-1

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Change to read:

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

▲and store at room temperature.▲*USP27*

Change to read:

Chromatographic purity—

■NOTE—For *Test 1* and *Test 2* the *System suitability solution, Standard solution,* and *Test solution* are to be refrigerated at or below 5° immediately after preparation and during analysis using a refrigerated autosampler. The solutions are stable at or below 5° for about 36 hours.■2S (*USP27*)

TEST 1—

Buffer solution—Prepare as directed in the *Assay.*

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (82:18). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

System suitability solution—Dissolve accurately weighed quantities of USP Zileuton RS and USP Zileuton Related Compound A RS in acetonitrile, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 5 µg of each USP Reference Standard per mL.

Standard solution—Dissolve an accurately weighed quantity of USP Zileuton RS in acetonitrile to obtain a solution having a known concentration of about 10 µg per mL.

Test solution—Transfer about 125 mg of Zileuton, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Chromatographic system—Prepare as directed in the *Assay,* except to use a flow rate of 2.2 mL per minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between zileuton and zileuton related compound A is not less than 1.5; and the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Zileuton taken by the formula:

$$100F(C_S / C_U)(r_i / r_S),$$

in which F is the relative response factor for each impurity, which is 1.0 for any peak with a relative retention time of 0.5, 0.7, 1.2, 1.6, 3.2, or 3.4, and is 1.2, 1.4, and 1.7 for peaks with relative retention times of 0.8, 2.1, and 2.8, respectively; C_S is the concentration, in mg per mL, of USP Zileuton RS in the *Standard solution;* C_U is the concentration, in mg per mL, of zileuton in the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for zileuton obtained from the *Standard solution:* not more than 0.1% of any individual impurity with a relative retention time of 0.7, 0.8, 1.6, 2.1, 3.2, or 3.4 is found; not more than 0.2% of any individual impurity with a relative retention time of 0.5 or 1.2 is found; and not more than 0.3% of any individual impurity with a relative retention time of 2.8 is found.

TEST 2—

Perchloric acid solution—Dissolve 5.0 mL of perchloric acid in 1000 mL of water.

Mobile phase—Prepare a filtered and degassed mixture of *Perchloric acid solution* and acetonitrile (1:1). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard stock solution—Dissolve an accurately weighed quantity of USP Zileuton Related Compound B RS in acetonitrile to obtain a solution having a known concentration of about 0.25 mg per mL. Transfer 5.0 mL of this solution to a 50-mL volumetric flask, dilute with acetonitrile to volume, and mix.

System suitability solution—Dissolve an accurately weighed quantity of USP Zileuton Related Compound C RS in acetonitrile to obtain a solution having a known concentration of about 10 µg per mL. Transfer 5.0 mL of this solution and 5.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with acetonitrile to volume, and mix.

Standard solution—Transfer 5.0 mL of the *Standard stock solution* to a 50-mL volumetric flask, dilute with acetonitrile to volume, and mix.

Test solution—Proceed as directed for *Test solution* under *Test 1.*

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between zileuton related compound B and zileuton related compound C is not less than 20. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5.0%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the major peaks. Calculate the percentage of each impurity in the portion of Zileuton taken by the formula:

$$100(C_S / C_U)(r_i / r_S),$$

in which C_S is the concentration, in mg per mL, of USP Zileuton Related Compound B RS in the *Standard solution;* C_U is the concentration, in mg per mL, of zileuton in the *Test solution;* r_i is the peak response for each impurity obtained from the *Test solution;* and r_S is the peak response for zileuton related compound B obtained from the *Standard solution:* not more than 0.1% of any individual impurity is found; and not more than 0.7% of total impurities is found, the results for *Test 1* and *Test 2* being added.

Change to read:

Assay—

■NOTE—The *Standard preparation* and the *Assay preparation* are to be refrigerated at or below 5° immediately after preparation and during analysis using a refrigerated autosampler. The solutions are stable at or below 5° for about 36 hours.■2S (*USP27*)

Buffer solution—Dissolve 7.7 g of ammonium acetate and 0.25 g of acetohydroxamic acid in about 900 mL of water in a 1000-mL volumetric flask, adjust with perchloric acid to a pH of 2.0, dilute with water to volume, and mix.

Mobile phase—Prepare a filtered and degassed mixture of *Buffer solution* and acetonitrile (72:28). Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Internal standard preparation—Transfer about 30 mg of methylparaben, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix.

Standard stock preparation—Dissolve an accurately weighed quantity of USP Zileuton RS in acetonitrile to obtain a solution having a known concentration of about 1 mg per mL.

Standard preparation—Transfer 5.0 mL of the *Standard stock preparation* and 4.0 mL of the *Internal standard preparation* to a 50-mL volumetric flask, dilute with acetonitrile to volume, and mix.

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Assay preparation—Transfer about 100 mg of Zileuton, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with acetonitrile to volume, and mix. Transfer 5.0 mL of this solution and 4.0 mL of the *Internal standard preparation* to a 50-mL volumetric flask, dilute with acetonitrile to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 30-cm column that contains 10-µm packing L1. The flow rate is about 1.5 mL per minute. Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between zileuton and methylparaben is not less than 5.0; the tailing factor is not more than 1.3; and the relative standard deviation for replicate injections is not more than 0.6%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Assay preparation* and the *Standard preparation* into the chromatograph, record the chromatograms, and measure the peak areas. Calculate the quantity, in mg, of $C_{11}H_{12}N_2O_2S$ in the portion of Zileuton taken by the formula:

$$1000C(R_U / R_S),$$

in which C is the concentration, in mg per mL, of USP Zileuton RS in the *Standard preparation;* and R_U and R_S are the peak area ratios obtained from the *Assay preparation* and the *Standard preparation,* respectively.

BRIEFING

Excipients, USP and NF Excipients, Listed by Category, *NF 21* page 2679 and page 1088 of *PF* 29(4)) [July–Aug. 2003]. The proposed revisions complement the proposed new monographs *Carbomer Homopolymer* and *Ammonio Methacrylate Copolymer Dispersion,* which appear elsewhere in this number of *PF.*

(EMC) RTS—37702-1; 39641-2

Change to read:

Antimicrobial Preservative
Benzalkonium Chloride
Benzalkonium Chloride Solution
Benzethonium Chloride
Benzoic Acid
Benzyl Alcohol
Butylparaben

▲Cetrimonium Bromide▲*NF22*
Cetylpyridinium Chloride
Chlorobutanol
Chlorocresol
Cresol
Ethylparaben
Methylparaben
Methylparaben Sodium
Phenol

■2-Phenoxyethanol■1S (*NF22*)
Phenylethyl Alcohol
Phenylmercuric Acetate
Phenylmercuric Nitrate
Potassium Benzoate
Potassium Sorbate
Propylparaben
Propylparaben Sodium
Sodium Benzoate
Sodium Dehydroacetate
Sodium Propionate
Sorbic Acid
Thimerosal
Thymol

Change to read:

Coating Agent

■Ammonio Methacrylate Copolymer Dispersion■2S (*NF22*)
Carboxymethylcellulose Sodium
Cellacefate (formerly Cellulose Acetate Phthalate)
Cellulose Acetate

■Cellulose Acetate Butyrate■1S (*NF22*)
Cellulose Acetate Phthalate (see Cellacefate)

■Copovidone■1S (*NF22*)

■Corn Syrup Solids■1S (*NF22*)
Ethylcellulose
Ethylcellulose Aqueous Dispersion
Gelatin
Glaze, Pharmaceutical
Hydroxypropyl Cellulose
~~Hydroxypropyl Methylcellulose~~
Hydroxypropyl Methylcellulose Phthalate (see Hypromellose Phthalate)

▲Hypromellose▲*NF22*

■Hypromellose Acetate Succinate■1S (*NF22*)
Hypromellose Phthalate (formerly Hydroxypropyl Methylcellulose Phthalate)
Methacrylic Acid Copolymer
Methacrylic Acid Copolymer Dispersion
Methylcellulose
Polyethylene Glycol
Polyvinyl Acetate Phthalate
Shellac

■Starch, Pregelatinized Modified■1S (*NF22*)
Sucrose
Titanium Dioxide
Wax, Carnauba
Wax, Microcrystalline
Zein

Change to read:

Emollient
Alkyl (C12-15) Benzoate

■Hydrogenated Soybean Oil■1S (*NF22*)

Change to read:

Emulsifying and/or Solubilizing Agent
Acacia
Cholesterol
Diethanolamine (Adjunct)

■Diethylene Glycol ~~Monostearates~~ Stearates■1S (*NF22*)

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■Ethylene Glycol ~~Monostearates~~ Stearates■1S (*NF22*)

▲Glyceryl Distearate▲*NF22*

▲Glyceryl Monolinoleate▲*NF22*

▲Glyceryl Monooleate▲*NF22*
Glyceryl Monostearate
Lanolin Alcohols
Lecithin
Mono- and Di-glycerides
Monoethanolamine (Adjunct)
Oleic Acid (Adjunct)
Oleyl Alcohol (Stabilizer)
Poloxamer
Polyoxyethylene 50 Stearate
Polyoxyl 35 Castor Oil
Polyoxyl 40 Hydrogenated Castor Oil

■Polyoxyl Lauryl Ether■1S (*NF22*)
Polyoxyl 10 Oleyl Ether
Polyoxyl 20 Cetostearyl Ether
Polyoxyl 40 Stearate

■Polyoxyl Stearyl Ether■1S (*NF22*)
Polysorbate 20
Polysorbate 40
Polysorbate 60
Polysorbate 80
Propylene Glycol Monostearate

■Sodium Cetostearyl Sulfate■1S (*NF22*)
Sodium Lauryl Sulfate
Sodium Stearate
Sorbitan Monolaurate
Sorbitan Monooleate
Sorbitan Monopalmitate
Sorbitan Monostearate
Stearic Acid
Trolamine
Wax, Emulsifying

Change to read:
Humectant

■Corn Syrup Solids■1S (*NF22*)
Glycerin
Hexylene Glycol
Propylene Glycol
Sorbitol

■Sorbitol, Anhydrized Liquid■1S (*NF22*)

Change to read:
Ointment Base
~~Caprylocaproyl Macrogolglycerides~~

■Caprylocaproyl Polyoxylglycerides■1S (*NF22*)
Diethylene Glycol Monoethyl Ether

■Lauroyl Macrogolglycerides■1S (*NF22*)
~~Lineoyl Macrogolglycerides~~

■Lineoyl Polyoxylglycerides■1S (*NF22*)
Lanolin
Ointment, Hydrophilic
Ointment, White
~~Oleoyl Macrogolglycerides~~

■Oleoyl Polyoxylglycerides■1S (*NF22*)
Ointment, Yellow
Polyethylene Glycol Ointment
Petrolatum
Petrolatum, Hydrophilic
Petrolatum, White
Rose Water Ointment
Squalane
~~Stearoyl Macrogolglycerides~~

■Stearoyl Polyoxylglycerides■1S (*NF22*)
Vegetable Oil, Hydrogenated, Type II

Change to read:
Plasticizer
Acetyltributyl Citrate
Acetyltriethyl Citrate
Castor Oil
Diacetylated Monoglycerides
Dibutyl Sebacate
Diethyl Phthalate
Glycerin
Polyethylene Glycol
Propylene Glycol

■Sorbitol, Anhydrized Liquid■1S (*NF22*)
Triacetin
Tributyl Citrate
Triethyl Citrate

Change to read:
Polymer Membrane
Cellulose Acetate

■Cellulose Acetate Butyrate■1S (*NF22*)

Change to read:
Solvent
Acetone
Alcohol
Alcohol, Diluted
Amylene Hydrate
Benzyl Benzoate
Butyl Alcohol
~~Caprylocaproyl Macrogolglycerides~~

■Caprylocaproyl Polyoxylglycerides■1S (*NF22*)
Corn Oil
Cottonseed Oil
Diethylene Glycol Monoethyl Ether
Ethyl Acetate
Glycerin
Hexylene Glycol
Isopropyl Alcohol

■Lauroyl Macrogolglycerides■1S (*NF22*)
~~Lineoyl Macrogolglycerides~~

■Lineoyl Polyoxylglycerides■1S (*NF22*)
Methyl Alcohol
Methylene Chloride
Methyl Isobutyl Ketone
Mineral Oil

~~Oleoyl Macrogolglycerides~~

■Oleoyl Polyoxylglycerides■1S (*NF22*)
Peanut Oil
Polyethylene Glycol
Propylene Glycol
Sesame Oil
~~Stearoyl Macrogolglycerides~~

■Stearoyl Polyoxylglycerides■1S (*NF22*)
Water for Injection
Water for Injection, Sterile
Water for Irrigation, Sterile
Water, Purified

Change to read:
Suspending and/or Viscosity-Increasing Agent
Acacia
Agar
Alginic Acid
Aluminum Monostearate
Attapulgite, Activated
Attapulgite, Colloidal Activated
Bentonite
Bentonite, Purified
Bentonite Magma
Carbomer 910
Carbomer 934
Carbomer 934P
Carbomer 940
Carbomer 941
Carbomer 1342

■Carbomer Homopolymer■2S (*NF22*)
Carboxymethylcellulose Calcium
Carboxymethylcellulose Sodium
Carboxymethylcellulose Sodium 12
Carrageenan
Cellulose, Microcrystalline, and Carboxymethylcellulose Sodium

■Corn Syrup Solids■1S (*NF22*)
Dextrin
Gelatin

■Gellan Gum■1S (*NF22*)
Guar Gum
Hydroxyethyl Cellulose
Hydroxypropyl Cellulose
~~Hydroxypropyl Methylcellulose~~

▲Hypromellose▲*NF22*
Magnesium Aluminum Silicate
Methylcellulose
Pectin
Polyethylene Oxide
Polyvinyl Alcohol
Povidone
Propylene Glycol Alginate
Silicon Dioxide
Silicon Dioxide, Colloidal
Sodium Alginate

▲Tapioca Starch▲*NF22*
Tragacanth
Xanthan Gum

Change to read:
Sweetening Agent
Aspartame

▲Aspartame Acesulfame▲*NF22*

■Corn Syrup Solids■1S (*NF22*)
Dextrates
Dextrose
Dextrose Excipient
Fructose

■Maltose■1S (*NF22*)
Mannitol
Saccharin
Saccharin Calcium
Saccharin Sodium
Sorbitol
Sorbitol Solution
Sucralose
Sucrose
Sugar, Compressible
Sugar, Confectioner's
Syrup

Change to read:
Tablet Binder
Acacia
Alginic Acid

■Carbomer Homopolymer■2S (*NF22*)
Carboxymethylcellulose, Sodium
Cellulose, Microcrystalline

■Copovidone■1S (*NF22*)

■Corn Syrup Solids■1S (*NF22*)
Dextrin
Ethylcellulose
Gelatin
Glucose, Liquid
Guar Gum

▲Hypromellose▲*NF22*

■Hypromellose Acetate Succinate■1S (*NF22*)
~~Hydroxypropyl Methylcellulose~~

■Maltose■1S (*NF22*)
Methylcellulose
Polyethylene Oxide
Povidone
Starch, Pregelatinized

■Starch, Pregelatinized Modified■1S (*NF22*)
Syrup

▲Tapioca Starch▲*NF22*

Change to read:
Tablet and/or Capsule Diluent
Calcium Carbonate
Calcium Phosphate, Dibasic
Calcium Phosphate, Tribasic

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Calcium Sulfate
Cellulose, Microcrystalline
Cellulose, Powdered

■Corn Syrup Solids■1S (*NF22*)
Dextrates
Dextrin
Dextrose Excipient
Fructose
Kaolin
Lactitol
Lactose

■Maltose■1S (*NF22*)
Mannitol
Sorbitol
Starch
Starch, Pregelatinized

■Starch, Pregelatinized Modified■1S (*NF22*)
Sucrose
Sugar, Compressible
Sugar, Confectioners

▲Tapioca Starch▲*NF22*

Change to read:
Tablet Disintegrant
Alginic Acid
Cellulose, Microcrystalline
Croscarmellose Sodium
Crospovidone

■Maltose■1S (*NF22*)
Polacrilin Potassium
Sodium Starch Glycolate
Starch
Starch, Pregelatinized

■Starch, Pregelatinized Modified■1S (*NF22*)

▲Tapioca Starch▲*NF22*

Change to read:
Tonicity Agent

■Corn Syrup Solids■1S (*NF22*)
Dextrose
Glycerin
Mannitol
Potassium Chloride
Sodium Chloride

Change to read:
Vehicle
FLAVORED AND/OR SWEETENED
Aromatic Elixir
Benzaldehyde Elixir, Compound

■Corn Syrup Solids■1S (*NF22*)
Peppermint Water
Sorbitol Solution
Syrup
OLEAGINOUS
Alkyl (C12-15) Benzoate
Almond Oil
Corn Oil
Cottonseed Oil
Ethyl Oleate
Isopropyl Myristate
Isopropyl Palmitate
Mineral Oil
Mineral Oil, Light
Octyldodecanol
Olive Oil
Peanut Oil
Safflower Oil
Sesame Oil
Soybean Oil
Squalane
SOLID CARRIER
Sugar Spheres
STERILE
Sodium Chloride Injection, Bacteriostatic
Water for Injection, Bacteriostatic

MONOGRAPHS (NF)

BRIEFING

Ammonio Methacrylate Copolymer Dispersion, page 628 of *PF* 28(2) [Mar.–Apr. 2002]. This new monograph, which previously appeared in *Pharmacopeial Previews,* is now forwarded to *In-Process* Revision. On the basis of comments received, the following changes have been included in the proposed monograph. A statement to include the use of antimicrobial preservatives and alkalizing agents is added to the Definition statement. A corresponding change is also made to the *Labeling* section. In the *Assay,* the following additional information is included for clarification: the initial temperature of the glacial acetic acid and the use of glacial acetic acid as the solvent to prepare the 0.6% cupric acetate solution.

(EMC: C. Sheehan; PSD: C. Okeke; NL: WL. Paul) RTS—37702-1

Add the following:

■Ammonio Methacrylate Copolymer Dispersion

» Ammonio Methacrylate Copolymer Dispersion is an aqueous dispersion of Ammonio Methacrylate Copolymer Type A or B in water. ~~It may contain surface-active agents.~~ It may contain suitable antimicrobial preservatives and alkalizing agents. The assay requirements differ for the two types, as set forth in the accompanying table.

	Ammonio methacrylate units, dried basis (%)	
Type	Min	Max
A	10.18	13.73
B	6.11	8.26

Packaging and storage—Preserve in tight containers, at a temperature not exceeding 25° for Type A, and not exceeding 30° for Type B. Protect from freezing.

Labeling—Label it to state whether it is Type A or Type B. Label it to indicate the name and quantity of any added antimicrobial preservative or alkalizing agent.

USP Reference standards ⟨11⟩—*USP Ammonio Methacrylate Copolymer Type A RS*. *USP Ammonio Methacrylate Copolymer Type B RS*.

Identification—

A: *Infrared Absorption* ⟨197K⟩—Proceed as directed, except to use the residue obtained in the test for *Loss on drying* as the test specimen.

B: It meets the requirements of the test for *Viscosity* and the *Assay.*

Viscosity ⟨911⟩—Use a viscosimeter equipped with a spindle having a cylinder 1.88 cm in diameter and 6.51 cm high attached to a shaft 0.32 cm in diameter. The distance from the top of the cylinder to the lower tip of the shaft is 0.75 cm, and the immersion depth is 8.15 cm. Adjust the temperature to 20 ± 0.10°. With the spindle rotating at 30 rpm, immediately record the scale reading. Multiply the scale reading by the constant for the viscosimeter spindle and speed employed, to obtain the viscosity in centipoises. The viscosity is not more than 100 centipoises.

Loss on drying ⟨731⟩—Dry it at 110° for 6 hours: it loses between 68.5% and 71.5% of its weight.

Residue on ignition ⟨281⟩—Using mild heating conditions (e.g., steam bath, sand bath, etc.) to avoid loss of material, evaporate the dispersion to dryness prior to ignition: not more than 0.5% of residue is obtained, calculated on the undried dispersion basis.

Limit of monomers—Proceed as directed in the test for *Limit of monomers* under *Ammonio Methacrylate Copolymer:* not more than 0.002% of methyl methacrylate and not more than 0.008% of ethyl acrylate are found.

Coagulum content—Accurately weigh a stainless steel sieve having 125-µm openings, and filter 100 g of Dispersion through it. Wash the sieve with distilled water until a clear filtrate is obtained, and dry the sieve to constant weight at 105°: the weight of the residue does not exceed 1000 mg (1%).

Assay—Dry under vacuum 2 g of Ammonio Methacrylate Copolymer Dispersion Type A, or 4 g of Ammonio Methacrylate Copolymer Dispersion Type B at 90° for 30 minutes. Dissolve in 75 mL of glacial acetic acid at about 50°, within about 30 minutes of drying. After the solution has cooled down, add 25 mL of 0.6% cupric acetate solution in glacial

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acetic acid, and titrate with 0.1 N perchloric acid VS, determining the end point potentiometrically. Perform a blank titration, and make any necessary correction. Each mL of 0.1 N perchloric acid is equivalent to 20.772 mg of ammonio methacrylate ($C_9H_{18}ClNO_2$) units.■2S (*NF22*)

BRIEFING

Carbomer 910, *NF 21* page 2704. It is proposed to delete this monograph because this product has been discontinued. See also the briefing under *Carbomer Homopolymer*.

(EMC: E. Gonikberg) RTS—39641-3

Delete the following:

■~~Carbomer 910~~

~~» Carbomer 910 is a high molecular weight polymer of acrylic acid cross-linked with allyl ethers of pentaerythritol. Carbomer 910, previously dried in vacuum at 80° for 1 hour, contains not less than 56.0 percent and not more than 68.0 percent of carboxylic acid (–COOH) groups. The viscosity of a neutralized 1.0 percent aqueous dispersion of Carbomer 910 is between 3000 and 7000 centipoises.~~

~~**Packaging and storage**—Preserve in tight containers.~~
~~**Labeling**—Label it to indicate that it is not intended for internal use.~~
~~**Viscosity**—Proceed as directed in the test for *Viscosity* under *Carbomer 934P*, except to perform the test on a 1.0% aqueous dispersion (prepared by using 5.00 g instead of 2.50 g) and to use a spindle having a disk 1.3 cm in diameter and 0.2 cm high attached to a shaft 0.32 cm in diameter, the distance from the top of the disk to the lower tip of the shaft being 2.4 cm and the immersion depth being 5 cm (No. 3 spindle). The viscosity is between 3000 and 7000 centipoises.~~
~~**Limit of benzene**—Proceed as directed in the test for *Limit of benzene* under *Carbomer 934P*, except to use about 20 mg of Carbomer 910, accurately weighed, instead of about 1 g of Carbomer 934P, to prepare the *Test solution*. Calculate the percentage of benzene in the portion of Carbomer 910 taken by the formula:~~

$$10(C/W)(r_U/r_S),$$

~~in which *C* is the concentration, in µg per mL, of benzene in the *Standard solution*, *W* is the weight, in mg, of Carbomer 910 taken to prepare the *Test solution*, and r_U and r_S are the benzene peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% is found.~~

~~**Other requirements**—It meets the requirements for *Identification*, *Loss on drying*, *Heavy metals*, and *Assay for carboxylic acid content* under *Carbomer 934P*.~~■2S (*NF22*)

BRIEFING

Carbomer Homopolymer, page 1276 of *PF* 28(4) [July–Aug. 2002]. This new monograph, which previously appeared in *Pharmacopeal Previews,* is now being forwarded to *In-Process Revision*. On the basis of comments received, it is proposed to change the scope of this new monograph to cover only Carbomer Homopolymers manufactured without the use of benzene. It is proposed to delete the test for *Limit of benzene* which is no longer applicable and to make changes in the *Definition, Labeling,* and *Viscosity* sections that are consistent with the new scope. It is also proposed to make changes in the *Identification* section. The currently official monographs for *Carbomers 934, 934P, 940,* and *941,* manufactured using benzene, will not be replaced by this new monograph as previously proposed. It is also proposed to delete the *Carbomer 910* monograph because this product is discontinued.

(EMC: E. Gonikberg; NL: C. Barnstein) RTS—39641-2

Add the following:

■Carbomer Homopolymer

» Carbomer Homopolymer is a high molecular weight polymer of acrylic acid cross-linked with polyalkenyl ethers of polyalcohols. Carbomer Homopolymer, previously dried, contains not less than 56.0 percent and not more than 68.0 percent of carboxylic acid (–COOH) groups.

NOTE—Carbomer Homopolymer is manufactured without the use of benzene. Specifically, ethyl acetate or a mixture of ethyl acetate and cyclohexane is used. Carbomer Homopolymer obtained from different manufacturers or produced in different solvents with different manufacturing

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processes may not have identical properties with respect to its use for specific pharmaceutical purposes, e.g., as tablet controlled-release agents, bioadhesives, topical gellants, etc. Therefore, types of Carbomer Homopolymer should not be interchanged unless performance equivalency has been ascertained.

Packaging and storage—Preserve in tight containers, at a temperature not exceeding 45°.

~~**USP Reference standards** ⟨11⟩ —*USP Carbomer Homopolymer RS.*~~

Labeling~~—The label states the nominal viscosity range of a defined neutralized dispersion; the solvent used in the polymerization process and residual level; and, where applicable, that the Carbomer Homopolymer has been slightly preneutralized.~~ Label it to indicate whether it is Type A, B, or C; and also to state the measured viscosity, the solvent or solvents used in the polymerization process, and the nominal and residual solvent levels for each solvent.

Identification—

~~**A:** *Infrared Absorption* ⟨197K⟩.~~

~~**B:** The viscosity test result complies with the viscosity range indicated on the label.~~

A: *Infrared Absorption* ⟨197K⟩—The IR spectrum exhibits main bands at or near (±5) wave numbers (cm^{-1}) 1710, 1454, 1414, 1245, 1172, 1115, and 801, with the strongest band at 1710.

~~**C:**~~ **B:** Adjust a 1 in 100 dispersion of it with 1 N sodium hydroxide to a pH of about 7.5: a viscous gel is produced.

~~**D:**~~ **C:** Add 2 mL of a 1 in 10 aqueous solution of calcium chloride, while stirring, to 10 mL of the gel obtained from *Identification* test ~~*C*~~ *B* a white precipitate is immediately produced.

~~**E:**~~ **D:** Prepare a 1 in 100 dispersion of it. Add 0.5 mL of thymol blue TS to 10 mL of the dispersion: an orange color is produced. To another 10 mL of the dispersion add 0.5 mL of cresol red TS: a yellow color is produced.

Viscosity ⟨911⟩—Carefully add 2.50 g of the resin, which has been previously dried, to 500 mL of water in a 800-mL beaker, while stirring continuously at 1000 ± 50 rpm. The stirrer shaft is set at an angle of 60° and positioned at one side of the beaker, and the propeller is positioned near the bottom of the beaker. The stirrer used should be a three-blade, 2-inch marine impeller. Add Carbomer Homopolymer at a uniform rate over a period of 45 to 60 seconds, being sure that loose aggregates of powder are broken up, and continue stirring at 1000 ± 50 rpm for 15 minutes. [NOTE—Proper dispersion of the Carbomer Homopolymer resin is imperative for accurate viscosity readings.] Remove the stirrer, and let the beaker containing the dispersion stand at controlled room temperature for 30 minutes. Insert a paddle stirrer to a depth necessary to ensure that the air is not drawn into the dispersion, and while stirring at 300 ± 25 rpm, titrate potentiometrically (see *Titrimetry* ⟨541⟩) with sodium hydroxide solution (18 in 100) to the pH indicated on the label. (For example, if the pH is 7.3, then the total volume of sodium hydroxide would be about 5.4 mL.) After adding the sodium hydroxide solution, stir with a paddle mixer at 300 ± 25 rpm for 2 to 3 minutes. [NOTE—After neutralization, care must be taken to avoid excessively high shearing, as aggressive mixing will break the polymer chains and reduce the viscosity reading.] Take the final pH reading with a pH meter. If the final pH exceeds that indicated on the label, discard the mucilage, and prepare another using a smaller amount of sodium hydroxide for titration. Place the neutralized mucilage into a water bath maintained at 25 ± 2° for 1 hour, then perform the viscosity determination without delay.

In-Process Revision

Equip a suitable rotational viscometer (i.e., a Brookfield RVT or RVF viscometer) with a suitable spindle, as defined in the chart below. For spindle dimensions, consult the table under *Carbomer Copolymer*.

Expected Viscosity (cP)	Spindle Number	Multiplier
100–400	1	5
400–1600	2	20
1000–4000	3	50
2000–8000	4	100
4000–16,000	5	200
10,000–40,000	6	500
40,000–160,000	7	2000

With the spindle rotating at 20 rpm, observe and record the scale reading. Calculate the viscosity, in centipoise, by multiplying the scale reading by the multiplier defined in the table above for the spindle used at 20 rpm. ~~Viscosity results for the type of Carbomer Homopolymer falls within the range specified in the label when measured at 25 ± 2° and 20 rpm.~~ The viscosity values, determined by the conditions specified herein, are within the limits specified in the accompanying table.

Carbomer Homopolymer	Viscosity Specified (cP)
A	4,000–11,000
B	25,000–45,000
C	40,000–60,000

Loss on drying ⟨731⟩—Dry it in vacuum at 80° for 1 hour: it loses not more than 3.0% of its weight.

Residue on ignition ⟨231⟩: not more than 4.0%, determined on 1.0 g.

Heavy metals, *Method II* ⟨231⟩: not more than 0.002%.

Limit of ethyl acetate and cyclohexane—[NOTE—This test is required only for those Carbomer Homopolymers whose labeling indicates that ethyl acetate or a mixture of ethyl acetate and cyclohexane was used in the polymerization process.]

Standard stock solution—Transfer 5.0 mL of methanol to a 10-mL serum vial, insert a rubber septum, and seal with a metal cap. Add an accurately weighed quantity of about 25.0 µL of ethyl acetate and 20.0 µL of cyclohexane through the septum into the vial, and mix.

Standard solution—Transfer 20.0 mL of methanol to a 30-mL serum vial, insert a rubber septum, and seal with a metal cap. Through the rubber septum, add 10 µL of methyl ethyl ketone (internal standard) and 50.0 µL of the *Standard stock solution*, and mix.

Test solution—Transfer about 50 mg of Carbomer Homopolymer, accurately weighed, to a 30-mL serum vial, add 20 mL of methanol, insert a rubber septum, and seal with a metal cap. Through the rubber septum, add 10 µL of methyl ethyl ketone, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—Proceed as directed under *Carbomer Copolymer*.

Procedure—Proceed as directed under *Carbomer Copolymer*, except to calculate the percentages of ethyl acetate and cyclohexane in the portion of Carbomer Homopolymer taken by the formula:

$$100(W_S / W_T)(R_U / R_S),$$

in which W_S is the weight, in mg, of ethyl acetate or cyclohexane, as appropriate, in the *Standard solution*; W_T is the weight, in mg, of Carbomer Homopolymer taken to prepare the *Test solution;* and R_U and R_S are the peak area ratios of the relevant analyte peak to the methyl ethyl ketone peak obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.5% of ethyl acetate and not more than 0.3% of cyclohexane is found.

In-Process Revision

Limit of benzene—[NOTE—This test is required only for those Carbomer Homopolymers whose labeling indicates that benzene was used in the polymerization process.]

Standard solution—Quantitatively dissolve an accurately weighed quantity of benzene in methanol to obtain a solution having a known concentration of about 0.2 mg per mL. Dilute this solution quantitatively with organic-free water (see *Organic Volatile Impurities* ⟨467⟩) to obtain a solution having a known concentration of about 1.0 µg per mL.

Test solution—Transfer an accurately weighed quantity of about 100 mg of Carbomer Homopolymer to a 100-mL volumetric flask. Add about 75 mL of sodium chloride solution (2 in 100), and mix by mechanical means until homogeneous (about 30 minutes). Dilute with sodium chloride solution (2 in 100) to volume, and mix until homogeneous (1 minute or less). [NOTE—This preparation must be analyzed within 3 hours of preparation.]

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector, a 0.53-mm × 30-m fused silica analytical column coated with a 3.0-µm G43 stationary phase, a 0.53-mm × 5-m silica guard column deactivated with phenylmethyl siloxane, and a splitless injection system. The carrier gas is helium flowing at a linear velocity of about 35 cm per second. The injection port and detector are maintained at 140° and 260°, respectively. The column temperature is programmed according to the following steps: it is held at 40° for 20 minutes after injection, then increased at 50° per minute to 260°, and held at 260° for 20 minutes. Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 15%.

Procedure—Separately inject equal volumes (about 4 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for the benzene peaks. Calculate the percentage of benzene in the portion of Carbomer Homopolymer taken by the formula:

$$10(C/W)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of benzene in the *Standard solution*; W is the weight, in mg, of Carbomer Homopolymer taken to prepare the *Test solution*; and r_U and r_S are the benzene peak responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.1% is found.

Limit of acrylic acid—

0.01 M Phosphate buffer—Dissolve 1.361 g of monobasic potassium phosphate in 100 mL of water, and mix.

Solution A—Use *0.01 M Phosphate buffer*.

Solution B— Prepare a filtered and degassed mixture of *0.01 M Phosphate buffer* and acetonitrile (1:1, v/v).

Mobile phase—Use variable mixtures of *Solution A* and *Solution B* as directed for *Chromatographic system*. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Solvent—Dissolve 25 g of potassium alum in 1000 mL of water, and mix.

Standard solution—Dissolve an accurately weighed quantity of acrylic acid in the *Solvent*, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 12.5 µg per mL.

Test solution—Mix about 100 mg of Carbomer Homopolymer, accurately weighed, with *Solvent*, and add *Solvent* to obtain 20.0 mL of suspension. Heat the suspension at 50° for 20 minutes with occasional shaking. Then shake the suspension continuously at room temperature for 60 minutes. Centrifuge and use the clear supernatant.

In-Process Revision

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 205-nm detector and a 4.6-mm × 12-cm column that contains packing L1. The flow rate is about 1 mL per minute. The chromatograph is programmed as follows.

Time (minutes)	*Solution A* (%)	*Solution B* (%)	Elution
0	100	0	equilibration
0–8	100	0	isocratic
8–9	100→0	0→100	linear gradient
9–20	0	100	isocratic
20–21	0→100	100→0	linear gradient
21–30	100	0	isocratic

Chromatograph the *Standard solution*, and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 5%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the response for the acrylic acid peaks. Calculate the percentage of free acrylic acid in the portion of Carbomer Homopolymer taken by the formula:

$$(C/W)(r_U/r_S),$$

in which C is the concentration, in µg per mL, of acrylic acid in the *Standard solution;* W is the weight, in mg, of Carbomer Homopolymer taken to prepare the *Test solution;* and r_U and r_S are the acrylic acid responses obtained from the *Test solution* and the *Standard solution*, respectively: not more than 0.25% is found.

Content of carboxylic acid—Slowly add about 400 mg of Carbomer Homopolymer, previously dried in vacuum at 80° for 1 hour and accurately weighed, to 400 mL of water in a 800-mL beaker, while stirring continuously at about 1000 rpm. The stirrer shaft is set at an angle of 60° and positioned at one side of the beaker, and the propeller is positioned near the bottom of the beaker. Continue stirring for 15 minutes. Reduce the stirring speed, and, using a calomel-glass electrode, titrate potentiometrically with 0.25 N sodium hydroxide VS to a pH of 10.0 (see *Titrimetry* ⟨541⟩). Allow 1 minute for mixing, after each addition of 0.25 N sodium hydroxide VS, before recording the pH. Calculate the percentage of carboxylic acid in the portion of Carbomer Homopolymer taken by the formula:

$$100(45.02VN/W),$$

in which V is the volume, in mL, of sodium hydroxide solution consumed; N is the normality of the sodium hydroxide solution; W is the weight, in mg, of Carbomer Homopolymer taken; and 45.02 is the molecular weight of the carboxylic acid (–COOH) group.■2S (*NF22*)

BRIEFING

Guar Gum, *NF 21* page 2770; **Xanthan Gum,** *NF 21* page 2861. It is proposed to correct an invalid reference in the test for *Lead*.

(EMC: D. Bempong) RTS—40418-1

Change to read:

Lead ⟨251⟩—Prepare a *Test Preparation* as directed ~~for organic compounds,~~

■in the chapter■2S (*NF22*)
and use 10 mL of *Diluted Standard Lead Solution* (10 µg of Pb) for the test: the limit is 0.001%.

In-Process Revision

BRIEFING

Magnesium Stearate, *NF 21* page 2787 and page 474 of *PF* 29(2) [Mar.–Apr. 2003]. On the basis of comments received, it is proposed to revise the test for *Specific surface area* to allow for plot deviations from linearity for P/P_0 values from 0.05 to 0.15.

(EMC: C. Sheehan) RTS—40327-1

Change to read:

Microbial limits ⟨61⟩—The total aerobic microbial count does not exceed 10^3 ~~per g~~

■cfu per g,■2S (*NF22*)
the total combined molds and yeasts count does not exceed ~~500 per g~~

■10^2 cfu per g,■2S (*NF22*)
and it meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli.*

Change to read:

Specific surface area ⟨846⟩—[NOTE—In cases where there are no functionality-related concerns regarding the specific surface area of this article, this test may be omitted.] Where the labeling states the specific surface area, determine the specific surface area value as directed in the chapter in the P/P_0 range of 0.05 to 0.15, and using outgassing conditions of 2 hours at 40°.

■If the plot deviates from linearity for P/P_0 values of 0.05 to 0.15, then a suitable range of P/P_0 values should be validated for linearity. In this case, it is necessary to state the range of validated P/P_0 values, the increment of the P/P_0 values, and the outgassing conditions employed.■2S (*NF22*)

BRIEFING

Methacrylic Acid Copolymer Dispersion, *NF 21* page 2792. It is proposed to revise the sample volume in the test for *Viscosity* to 16 mL because comments were received that commercially available low-viscosity adapters cannot hold the 20-mL sample. The dimensions of the viscosimeter are also provided.

(EMC: D. Bempong) RTS—40250-1

Change to read:

Viscosity ⟨911⟩—~~Use a rotational viscosimeter equipped with a low-viscosity adapter. Mix the Dispersion, and pipet 20 mL of it into the low-viscosity small sample adapter. Adjust the temperature to 20 ± 0.1°. With the spindle rotating at 30 rpm, immediately~~ observe and record the scale reading. Multiply the scale reading by the constant for the adapter and spindle speed employed to obtain the viscosity in centipoises. The viscosity is not more than 15 centipoises.

■Equip a suitable rotational viscosimeter with an adapter system consisting of a measuring cylinder and a spindle. The measuring cylinder has an internal diameter of 2.762 cm and a depth of 13.50 cm; the spindle is 2.515 cm in diameter and 9.074 cm in height, and has a shaft that is 0.40 cm in diameter. Mix the Dispersion, pipet 16 mL of it into the measuring cylinder, and adjust the temperature of the dispersion and the adapter to 20 ± 0.1°. With the spindle rotating at 30 rpm, immediately observe and record the scale reading. Convert the scale reading to centipoises by multiplying the reading by the constant for the viscosimeter, the adapter system, and the speed employed. The viscosity is not more than 15 centipoises.■2S (*NF22*)

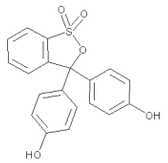
BRIEFING

Phenolsulfonphthalein, page 1899 of *PF* 28(6) [Nov.–Dec. 2002]. On the basis of comments received, it is proposed to revise the *Labeling* and *Bacterial endotoxins* sections to reflect usage of this excipient in parenteral articles. It is also proposed to add storage conditions to the *Packaging and storage* section. In addition, editorial style changes have been made.

(EMC: E. Gonikberg; VVI: L. Bhattacharyya) RTS—40020-3

Add the following:

■Phenolsulfonphthalein



$C_{19}H_{14}O_5S$ 354.38

Phenol Red

In-Process Revision

Phenol, 4,4′-(3*H*-2,l-benzoxathiol-3-ylidene)bis-,(*S*,*S*-dioxide).

3,3-bis(4-hydroxyphenyl)-3*H*-2,l-benzoxathiole 1,1-dioxide [*143-74-8*].

» Phenolsulfonphthalein contains not less than 98.0 percent and not more than 102.0 percent of $C_{19}H_{14}O_5S$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers. Store at 25°, excursions permitted between 15° and 30°.

Labeling—Where it is intended for use in ~~vaccines administered either intramuscularly or subcutaneously,~~ articles administered parenterally, it is so labeled.

USP Reference standards ⟨11⟩—*USP Endotoxin RS.*

Identification—

A: Transfer 5 mg of Phenolsulfonphthalein to a 100-mL volumetric flask, dissolve in and dilute with sodium carbonate solution (1 in 100) to volume, and mix. Dilute 5.0 mL of the solution so obtained to 100.0 mL with sodium carbonate solution (1 in 100). Examined between 400 and 630 nm, the solution exhibits an absorption maximum at 558 nm. The specific absorbance at the maximum is between 1900 and 2100.

B: Dissolve about 10 mg of Phenolsulfonphthalein in 2 mL of 1 N sodium hydroxide, and add 8 mL of water. To 5 mL of the solution so obtained add 1 mL of 0.1 N potassium bromide-bromate and 1 mL of diluted hydrochloric acid, shake, and allow to stand for 15 minutes. Render the solution alkaline with 1 N sodium hydroxide: an intense violet-blue color is produced.

Visual transition interval—Dissolve 1.0 g of potassium chloride in 100 mL of water, and adjust with 0.01 N hydrochloric acid or sodium hydroxide to a pH of 6.8. Dissolve 0.1 g of Phenolsulfonphthalein in 100 mL of alcohol, and add 0.15 mL of this solution to the potassium chloride solution. The color of the resulting solution is yellow, with not more than a faint trace of green color. Titrate the solution with 0.01 N sodium hydroxide to a pH of 7.0: the color of the solution becomes orange. Continue the titration to pH 8.2: the color of the solution becomes red. Not more than 0.20 mL of 0.01 N sodium hydroxide is consumed in the entire titration.

Microbial limit ⟨61⟩—The total aerobic microbial count does not exceed 10^3 microorganisms per g, and the total combined molds and yeasts count does not exceed 100 cfu per g.

Bacterial endotoxins ⟨85⟩—Where it is intended for use in ~~vaccines administered either intramuscularly or subcutaneously,~~ articles administered parenterally, it contains not more than 600 USP Endotoxin Units per mg.

Loss on drying ⟨731⟩—Dry 1 g of the powdered Phenolsulfonphthalein at 105° to constant weight: it loses not more than 1.0% of its weight.

Residue on ignition ⟨281⟩: not more than 0.2%, determined on a 0.5-g portion.

Insoluble substances—To about 1 g of the finely powdered Phenolsulfonphthalein, accurately weighed, add a solution of 0.50 g of sodium bicarbonate in 12 mL of water. Allow to stand for 1 hour, shaking frequently. Dilute with sufficient water to make 100 mL, and allow to stand for 15 hours. Centrifuge at 2000 to 3000 *g* for 30 minutes, and decant the supernatant. Wash the residue first with 25 mL of sodium bicarbonate solution (1 in 100), then with 25 mL of

water, and dry at 105°: the weight of the insoluble residue does not exceed 0.5% of the weight of Phenolsulfonphthalein taken.

Chromatographic purity—

Adsorbent: 0.25-mm layer of chromatographic silica gel mixture.

Application volume: l0 µL

Developing solvent system: a mixture of *tert*-amyl alcohol, glacial acetic acid, and water (100:25:25).

Test solution—Transfer about 100 mg of Phenolsulfonphthalein to a 5-mL volumetric flask, dissolve in and dilute with 0.1 N sodium hydroxide to volume, and mix.

Diluted test solution—Transfer 0.5 mL of the *Test solution* to a 100-mL volumetric flask, dilute with 0.1 N sodium hydroxide to volume, and mix.

Procedure—Proceed as directed for *Thin-Layer Chromatography* under *Chromatography* ⟨621⟩. Allow the plate to air-dry until the solvent has evaporated, and expose the plate to ammonia vapor. Examine the plate under short-wavelength UV light. Not more than one spot, apart from the principal spot, appears in the chromatogram obtained from the *Test solution.* This spot is not more intense than the spot in the chromatogram obtained from the *Diluted test solution:* not more than 0.5% is found.

Assay—Transfer about 0.9 g of Phenolsulfonphthalein, accurately weighed, to a 250-mL volumetric flask, dissolve in 15 mL of 1 N sodium hydroxide, dilute with water to volume, and mix. Transfer 10.0 mL of the solution so obtained to a glass-stoppered flask, add 25 mL of glacial acetic acid, 20.0 mL of 0.1 N potassium bromate VS, 5 mL of potassium bromide solution (1 in 10), and 5 mL of hydrochloric acid, and immediately insert the stopper into the flask. Allow to stand protected from light for 15 minutes. Quickly add 10 mL of potassium iodide solution (1 in 10), taking care to avoid the escape of bromine vapor, immediately insert the stopper in the flask, and shake vigorously. Rinse the stopper and the neck of the flask with a small quantity of water, and titrate the liberated iodine with 0.1 N sodium thiosulfate VS, using starch TS as the indicator. Perform a blank determination (see *Residual Titrations* under *Titrimetry* ⟨541⟩), and note the difference in volumes required. Each mL of the difference in volumes of 0.1 N sodium thiosulfate is equivalent to 4.43 mg of $C_{19}H_{14}O_5S$.■2S (*NF22*)

BRIEFING

Poloxamer, *NF 21* page 2809. On the basis of comments received, it is proposed to revise the preparation of the *Phthalic anhydride–pyridine solution* in the *Average molecular weight* determination because the desired concentration of phthalic anhydride is not obtained using the current procedure. Instead of adding 144 g of phthalic anhydride to 1000 mL of pyridine, it is proposed to dissolve the phthalic anhydride sample in pyridine, and then dilute this solution with pyridine to 1000 mL.

(EMC: D. Bempong) RTS—40381-1

Change to read:

Average molecular weight—

Phthalic anhydride–pyridine solution— ~~Add 144 g of phthalic anhydride to 1000 mL of freshly opened or freshly distilled pyridine containing less than 0.1% of water. Protect from light. Shake vigorously until completely dissolved, and allow to stand overnight.~~

■Dissolve 144 g of phthalic anhydride in freshly opened or freshly distilled pyridine containing less than 0.1% of water, and dilute with pyridine to 1000 mL. Protect from light, and allow to stand overnight.■2S (*NF22*)

In-Process Revision

To verify that the *Phthalic anhydride–pyridine solution* has adequate strength, pipet 10 mL into a 250-mL conical flask, add 25 mL of pyridine and 50 mL of water, and after about 15 minutes add 0.5 mL of a solution of phenolphthalein in pyridine (1 in 100), then titrate with 0.5 N sodium hydroxide VS: it consumes between 37.6 mL and 40.0 mL of 0.5 N sodium hydroxide.

Procedure—Accurately weigh a suitable quantity, not exceeding 15 g, of Poloxamer, calculated by multiplying the average molecular weight by 0.004, into a glass-stoppered, 250-mL boiling flask. Carefully pipet 25 mL of *Phthalic anhydride–pyridine solution* into the flask, touching the tip of the drained pipet to the protrusion in the flask. Add a few glass beads, and swirl to dissolve the specimen. Pipet 25 mL of *Phthalic anhydride–pyridine solution* into a second, glass-stoppered, conical flask, add a few glass beads, and use as the reagent blank. (An additional 25-mL portion of pyridine may be added to both the test specimen and reagent blank, prior to refluxing, if necessary to ensure fluidity.) Heat both flasks, fitted with suitable reflux condensers, and allow to reflux for 1 hour. Allow to cool, and pour two 10-mL portions of pyridine through each condenser. Remove the flasks from the condensers, add 10 mL of water to each, insert the stoppers, swirl, and allow to stand for 10 minutes. To each flask add 50.0 mL of 0.66 N sodium hydroxide and 0.5 mL of a 1 in 100 solution of phenolphthalein in pyridine. Titrate with 0.5 N sodium hydroxide VS to a light pink endpoint that persists for not less than 15 seconds, recording the volume, in mL, consumed by the residual acid in the test solution as *S,* and that consumed by the blank as *B*. Calculate the average molecular weight taken by the formula:

$$2000W/[(B - S)(N)],$$

in which W is the weight, in g, of the test specimen taken; and N is the exact normality of the 0.5 N sodium hydroxide VS.

BRIEFING

Stearyl Alcohol, *NF 21* page 2844. On the basis of comments received, it is proposed to revise the *System suitability solution* in the *Assay* to use dehydrated alcohol instead of alcohol to be consistent with the use of dehydrated alcohol in the *Assay preparation.*

(EMC: C. Sheehan) RTS—40338-01

Change to read:

Assay—

System suitability solution—Dissolve accurately weighed quantities of USP Stearyl Alcohol RS and USP Cetyl Alcohol RS in

■dehydrated■2S (*NF22*)
alcohol to obtain a solution containing about 9 mg per mL and 1 mg per mL, respectively.

Assay preparation—Dissolve 100 mg of Stearyl Alcohol in 10.0 mL of dehydrated alcohol, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The gas chromatograph is equipped with a flame-ionization detector and a 3-mm × 2-m column packed with 10% liquid phase G2 on support S1A. The carrier gas is helium. The temperature of the column is maintained at about 205°, the injection port temperature is maintained at about 275°, and the detector is maintained at about 250°. Chromatograph the *System suitability solution*, and record the peak responses as directed for *Procedure:* the resolution, *R,* between cetyl alcohol and stearyl alcohol is not less than 4.0; and the relative standard deviation for replicate injections is not more than 1.5%.

Procedure—Inject about 2 µL of the *Assay preparation* into the chromatograph, record the chromatogram, and measure the areas for the major peaks. Calculate the percentage of $C_{18}H_{38}O$ in the portion of Stearyl Alcohol taken by the formula:

$$100(r_U/r_s),$$

in which r_U is the peak area for stearyl alcohol obtained from the *Assay preparation;* and r_s is the sum of the areas of all the peaks except the solvent peak.

BRIEFING

Xanthan Gum, *NF 21* page 2861—See briefing under *Guar Gum*.

(EMC: D. Bempong) RTS—40417-1

Change to read:

Lead ⟨251⟩—Prepare a *Test Preparation* as directed ~~for organic compounds,~~

■in the chapter■2S (*NF22*)
and use 5 mL of *Diluted Standard Lead Solution* (5 µg of Pb) for the test: the limit is 5 µg per g.

In-Process Revision

GENERAL CHAPTERS

General Tests and Assays

General Requirements for Tests and Assays

BRIEFING

⟨**11**⟩ **Reference Standards,** *USP 26* page 1966, page 3131 of the *Second Supplement,* page 3212 of *PF* 22(6) [Nov.–Dec. 1996], page 4500 of *PF* 23(4) [July–Aug. 1997], page 5180 of *PF* 23(6) [Nov.–Dec. 1997], page 6925 of *PF* 24(5) [Aug.–Sept. 1998], page 8222 of *PF* 25(3) [May–June 1999], page 8561 of *PF* 25(4) [July–Aug. 1999], page 8893 of *PF* 25(5) [Sept.–Oct. 1999], page 9222 of *PF* 25(6) [Nov.–Dec. 1999], page 218 of *PF* 26(1) [Jan.–Feb. 2000], page 471 of *PF* 26(2) [Mar.–Apr. 2000], page 793 of *PF* 26(3) [May–June 2000], page 1369 of *PF* 26(5) [Sept.–Oct. 2000], page 1606 of *PF* 26(6) [Nov.–Dec. 2000], page 1832 of *PF* 27(1) [Jan.–Feb. 2001], page 2268 of *PF* 27(2) [Mar.–Apr. 2001], page 2594 of *PF* 27(3) [May–June 2001], page 2806 of *PF* 27(4) [July–Aug. 2001], page 3071 of *PF* 27(5) [Sept.–Oct. 2001], page 3348 of *PF* 27(6) [Nov.–Dec. 2001], page 111 of *PF* 28(1) [Jan.–Feb. 2002], page 433 of *PF* 28(2) [Mar.–Apr. 2002], page 839 of *PF* 28(3) [May–June 2002], page 1224 of *PF* 28(4) [July–Aug. 2002], page 1468 of *PF* 28(5) [Sept.–Oct. 2002], page 1913 of *PF* 28(6) [Nov.–Dec. 2002], page 163 of *PF* 29(1) [Jan.–Feb. 2003], page 483 of *PF* 29(2) [Mar.–Apr. 2003], page 710 of *PF* 29(3) [May–June 2003], page 1137 of *PF* 29(4) [July–Aug. 2003], and page 1601 of *PF* 29(5) [Sept.–Oct. 2003].

(HDQ) RTS—38539-2; 39641-2; 40086-1; 34256-1; 40415-2; 39437-1; 39468-2; 40025-1; 40225-1; 40393-1

In-Process Revision

Add the following:

■**USP Human Albumin RS**—[To come.]■2S (*USP27*)

Add the following:

■**USP Enoxaparin Sodium RS.**■2S (*USP27*)

Add the following:

■**USP Enoxaparin Sodium Solution for Bioassay RS.**■2S (*USP27*)

Add the following:

■**USP Glimepiride RS**—[To come.]■2S (*USP27*)

Add the following:

■**USP Glimepiride Related Compound A RS** [glimepiride *cis*-isomer]—[To come.]■2S (*USP27*)

Add the following:

■**USP Glimepiride Related Compound B RS** [glimepiride sulfonamide]—[To come.]■2S (*USP27*)

Add the following:

■**USP Glimepiride Related Compound C RS** [glimepiride urethane]—[To come.]■2S (*USP27*)

Add the following:

■**USP Glimepiride Related Compound D RS** [glimepiride 3-isomer]—[To come.]■2S (*USP27*)

Add the following:

■**USP Hemoglobin RS**—[To come.]■2S (*USP27*)

Add the following:

■**USP Low-Molecular-Weight Heparin Molecular Weight RS**—[To come.]■2S (*USP27*)

Add the following:

■**USP Metformin Hydrochloride RS**—Do not dry. Keep container tightly closed. Store in a refrigerator. Keep away from alkali.■2S (*USP27*)

Add the following:

■**USP Metformin Related Compound A RS** [1-cyanoguanidine]—Do not dry. Keep container tightly closed. Store in a refrigerator. Keep away from alkali.■2S (*USP27*)

Delete the following:

~~■**USP Methylphenidate Hydrochloride Erythro Isomer RS**—Do not dry before using. Keep container tightly closed.~~■2S (*USP27*)

Add the following:

■**USP Methylphenidate Hydrochloride Erythro Isomer Solution RS**—Keep container tightly closed.■2S (*USP27*)

Add the following:

■**USP Propofol RS.**■2S (*USP27*)

Add the following:

■**USP Propofol Resolution RS** [propofol and 2-isopropyl-6-*n*-propylphenol].■2S (*USP27*)

Add the following:

■**USP Propofol Related Compound A RS** [3,3′-5,5′-tetraisopropyldiphenol].■2S (*USP27*)

Add the following:

■**USP Propofol Related Compound B RS** [2,6-diisopropylbenzoquinone].■2S (*USP27*)

Add the following:

■**USP Propofol for System Suitability RS** [propofol, 3,3′-5,5′-tetraisopropyldiphenol and 2-(1-methylethoxy)-1,3-bis(1-methylethyl)benzene].■2S (*USP27*)

Physical Tests and Determinations

BRIEFING

⟨**621**⟩ **Chromatography,** *USP 26* page 2126, page 3154 of the *Second Supplement*, and page 1606 of *PF* 29(5) [Sept.–Oct. 2003]. It is proposed to add the descriptions for the chromatographic columns used in the section *Molar ratio of sulfate to carboxylate* in the monograph for *Enoxaparin Sodium* and in the test for *Free sulfate content* in the monograph for *Enoxaparin Sodium Injection*, that appear elsewhere in this number of *PF*. The column G49 is being proposed for deletion.

(HDQ: M. Marques) RTS—99380-01

Change to read:

CHROMATOGRAPHIC REAGENTS

The following list of packings (L), phases (G), and supports (S) is intended to be a convenient reference for the chromatographer. [NOTE—Particle sizes given in this listing are those generally provided. Where other, usually finer, sizes are required, the individual monograph specifies the desired particle size. Within any category of packings or phases listed below, there may be a wide range of columns available. Where it is necessary to define more specifically the chromatographic conditions, the individual monograph so indicates.]

Packings

L1—Octadecyl silane chemically bonded to porous silica or ceramic micro-particles, 3 to 10 µm in diameter.

L2—Octadecyl silane chemically bonded to silica gel of a controlled surface porosity that has been bonded to a solid spherical core, 30 to 50 µm in diameter.

L3—Porous silica particles, 5 to 10 µm in diameter.

L4—Silica gel of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L5—Alumina of controlled surface porosity bonded to a solid spherical core, 30 to 50 µm in diameter.

L6—Strong cation-exchange packing–sulfonated fluorocarbon polymer coated on a solid spherical core, 30 to 50 µm in diameter.

L7—Octylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L8—An essentially monomolecular layer of aminopropylsilane chemically bonded to totally porous silica gel support, 10 µm in diameter.

L9—10-µm irregular or spherical, totally porous silica gel having a chemically bonded, strongly acidic cation-exchange coating.

L10—Nitrile groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L11—Phenyl groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L12—A strong anion-exchange packing made by chemically bonding a quaternary amine to a solid silica spherical core, 30 to 50 µm in diameter.

L13—Trimethylsilane chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L14—Silica gel 10 µm in diameter having a chemically bonded, strongly basic quaternary ammonium anion-exchange coating.

L15—Hexylsilane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

L16—Dimethylsilane chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L17—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the hydrogen form, 7 to 11 µm in diameter.

L18—Amino and cyano groups chemically bonded to porous silica particles, 3 to 10 µm in diameter.

L19—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the calcium form, about 9 µm in diameter.

L20—Dihydroxypropane groups chemically bonded to porous silica particles, 5 to 10 µm in diameter.

L21—A rigid, spherical styrene-divinylbenzene copolymer, 5 to 10 µm in diameter.

L22—A cation-exchange resin made of porous polystyrene gel with sulfonic acid groups, about 10 µm in size.

L23—An anion-exchange resin made of porous polymethacrylate or polyacrylate gel with quaternary ammonium groups, about 10 µm in size.

L24—A semi-rigid hydrophilic gel consisting of vinyl polymers with numerous hydroxyl groups on the matrix surface, 32 to 63 µm in diameter.[5]

L25—Packing having the capacity to separate compounds with a molecular weight range from 100–5000 (as determined by polyethylene oxide), applied to neutral, anionic, and cationic water-soluble polymers. A polymethacrylate resin base, cross-linked with polyhydroxylated ether (surface contained some residual carboxyl functional groups) was found suitable.

L26—Butyl silane chemically bonded to totally porous silica particles, 5 to 10 µm in diameter.

L27—Porous silica particles, 30 to 50 µm in diameter.

L28—A multifunctional support, which consists of a high purity, 100 Å, spherical silica substrate that has been bonded with anionic exchanger, amine functionality in addition to a conventional reversed phase C8 functionality.

L29—Gamma alumina, reverse-phase, low carbon percentage by weight, alumina-based polybutadiene spherical particles, 5 µm in diameter with a pore volume of 80 Å.

L30—Ethyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.

[5] Available as ~~Fractogel TSK HW 40F and distributed by Merck and Co.~~ ■YMC-Pack PVA-SIL manufactured by YMC Co., Ltd.■1S (*USP27*)

In-Process Revision

L31—A strong anion-exchange resin-quaternary amine bonded on latex particles attached to a core of 8.5-µm macroporous particles having a pore size of 2000 Å and consisting of ethylvinylbenzene cross-linked with 55% divinylbenzene.

L32—A chiral ligand-exchange packing–L-proline copper complex covalently bonded to irregularly shaped silica particles, 5 to 10 µm in diameter.

L33—Packing having the capacity to separate ■dextrans■1S (*USP26*) by molecular size over a range of 4,000 to ■500,000■1S (*USP26*) Da. It is spherical, silica-based, and processed to provide pH stability.■[6] ■1S (*USP26*)

L34—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the lead form, about 9 µm in diameter.

L35—A zirconium-stabilized spherical silica packing with a hydrophilic (diol-type) molecular monolayer bonded phase having a pore size of 150 Å.

L36—A 3,5-dinitrobenzoyl derivative of L-phenylglycine covalently bonded to 5-µm aminopropyl silica.

L37—Packing having the capacity to separate proteins by molecular size over a range of 2,000 to 40,000 Da. It is a polymethacrylate gel.

L38—A methacrylate-based size-exclusion packing for water-soluble samples.

L39—A hydrophilic polyhydroxymethacrylate gel of totally porous spherical resin.

L40—Cellulose tris-3,5-dimethylphenylcarbamate coated porous silica particles, 5 to 20 µm in diameter.

L41—Immobilized α_1-acid glycoprotein on spherical silica particles, 5 µm in diameter.

L42—Octylsilane and octadecylsilane groups chemically bonded to porous silica particles, 5 µm in diameter.

L43—Pentafluorophenyl groups chemically bonded to silica particles

■by a propyl spacer,■1S (*USP27*)
5 to 10 µm in diameter.

L44—A multifunctional support, which consists of a high purity, 60 Å, spherical silica substrate that has been bonded with a cationic exchanger, sulfonic acid functionality in addition to a conventional reversed phase C8 functionality.

L45—Beta cyclodextrin bonded to porous silica particles, 5 to 10 µm in diameter.

L46—Polystyrene/divinylbenzene substrate agglomerated with quaternary amine functionalized latex beads, 10 µm in diameter.

L47—High-capacity anion-exchange microporous substrate, fully functionalized with trimethlyamine groups, 8 µm in diameter.[7]

L48—Sulfonated, cross-linked polystyrene with an outer layer of submicron, porous, anion-exchange microbeads, 15 µm in diameter.

L49—A reversed-phase packing made by coating a thin layer of polybutadiene onto spherical porous zirconia particles, 3 to 10 µm in diameter.[8]

L50—Multifunction resin with reversed-phase retention and strong anion-exchange functionalities. The resin consists of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm in diameter, and a surface area not less than 350 m^2 per g. Substrate is coated with quaternary ammonium functionalized latex particles consisting of styrene cross-linked with divinylbenzene.[9]

▲L51—Amylose tris-3,5-dimethylphenylcarbamate-coated, porous, spherical, silica particles, 5 to 10 µm in diameter.[10] ▲*USP26*

▲L52—A strong cation exchange resin made of porous silica with sulfopropyl groups, 5 to 10 µm in diameter.[11] ▲*USP26*

■L53—Weak cation-exchange resin consisting of ethylvinylbenzene, 55% cross-linked with divinylbenzene copolymer, 3 to 15 µm diameter. Substrate is surface grafted with carboxylic acid and/or phosphoric acid functionalized monomers. Capacity not less than 500 µEq/column.[12] ■1S (*USP26*)

■L54—A size exclusion medium made of covalent bonding of dextran to highly cross-linked porous agarose beads, about 13 µm in diameter.[13] ■2S (*USP26*)

▲L55—A strong cation-exchange resin made of porous silica coated with polybutadiene–maleic acid copolymer, about 5 µm in diameter.[14] ▲*USP27*

▲L56—Propyl silane chemically bonded to totally porous silica particles, 3 to 10 µm in diameter.[15] ▲*USP27*

■L~~53~~ ## (Alendronic Acid Tablets, PRP-X100)—An anion-exchange resin consisting of a rigid, spherical styrene-divinylbenzene copolymer with trimethylammonium groups at a loading of about 2 mEq per g, 3 to 20 µm in diameter.[a] ■1S (*USP27*)

■L~~54~~ ## (Maltose, Aminex HPX-87N)—Strong cation-exchange resin consisting of sulfonated cross-linked styrene-divinylbenzene copolymer in the sodium form, about 7 to 11 µm in diameter.[b] ■1S (*USP27*)

[6] Available as TSKgel G4000 SWXL from TosoHaas (www.tosohaas.com).

[7] Available as CarboPac MA1 and distributed by Dionex Corporation.

[8] Available as Zirchrom PBD, manufactured by ZirChrom Separations, Inc., distributed by Alltech, www.Alltechweb.com.

[9] Available as OmniPac PAX-500 and distributed by Dionex Corporation.

[10] Available as Chiralpak AD from Chiral Technologies, Inc., 730 Springdale Drive, P.O. Box 564, Exton, PA 19341.

[11] Available as TSK IC SW Cation from TosoHaas.

[12] Available as IonPac CS14 distributed by Dionex Corporation (www.dionex.com).

[13] Available as Superdex Peptide HR 10/30 from Amersham Pharmacia Biotech (www.amershambiosciences.com).

[14] Available as IC-Pak C M/D from Waters Corp. (www.waters.com).

[15] Available as Zorbax SB-C3 from Agilent Technologies. (www.agilent.com/chem)

[a] Available as PRP-X100 from Hamilton Company (www.hamiltoncompany.com).

[b] Available as Aminex HPX-87N from Bio-Rad Laboratories, (2000/01 catalog, #125-0143), Group Headquarters, Bio-Rad Laboratories, 2000 Alfred Nobel Dr., Hercules, California 94547 (www.discover.bio-rad.com).

In-Process Revision

■L~~57~~ ## (Nevirapine, Supelcosil ABZ)—Spherical, porous silica gel, 3 or 5 µm in diameter, the surface of which has been covalently modified with palmitamidopropyl groups and endcapped with acetamidopropyl groups to a ligand density of about 6 µmoles per m^2.[c] ■1S (*USP27*)

■L~~58~~ ## (Albumin Human, TSKgel G3000 SW)—Packing having the capacity to separate proteins by molecular weight over the range of 10 to 500 kDa. It is spherical (10 µm), silica-based, and processed to provide hydrophilic characteristics and pH stability.[d] ■1S (*USP27*)

■L~~61~~ ## (Lycopene, Lycopene Preparation, YMC 30)—C30 silane bonded phase on a fully porous spherical silica, 3 to 15 µm in diameter. ■1S (*USP27*)

■L## (Clopidogrel Bisulfate, Ultron ES-OVM)—A chiral-recognition protein, ovomucoid, chemically bonded to silica particles, about 5 µm in diameter, with a pore size of 120 Å. ■2S (*USP27*)

■L## (Enoxaparin Sodium Injection, IonPac AG11)—[To come.] ■2S (*USP27*)

■L## (Enoxaparin Sodium Injection, IonPac AS11)—[To come.] ■2S (*USP27*)

■L## (Enoxaparin Sodium, Dowex 1X8)—[To come.] ■2S (*USP27*)

■L## (Enoxaparin Sodium, Dowex 50WX2)—[To come.] ■2S (*USP27*)

Phases

G1—Dimethylpolysiloxane oil.
G2—Dimethylpolysiloxane gum.
G3—50% Phenyl-50% methylpolysiloxane.
G4—Diethylene glycol succinate polyester.
G5—3-Cyanopropylpolysiloxane.
G6—Trifluoropropylmethylpolysiloxane.
G7—50% 3-Cyanopropyl-50% phenylmethylsilicone.
G8—80% Bis(3-cyanopropyl)-20% 3-cyanopropylphenylpolysiloxane (percentages refer to molar substitution).
G9—Methylvinylpolysiloxane.
G10—Polyamide formed by reacting a C_{36} dicarboxylic acid with 1,3-di-4-piperidylpropane and piperidine in the respective mole ratios of 1.00:0.90:0.20.
G11—Bis(2-ethylhexyl) sebacate polyester.
G12—Phenyldiethanolamine succinate polyester.
G13—Sorbitol.
G14—Polyethylene glycol (av. mol. wt. of 950 to 1050).
G15—Polyethylene glycol (av. mol. wt. of 3000 to 3700).
G16—Polyethylene glycol compound (av. mol. wt. about 15,000). A high molecular weight compound of polyethylene glycol with a diepoxide linker. Available commercially as Polyethylene Glycol Compound 20M, or as Carbowax 20M, from suppliers of chromatographic reagents.
G17—75% Phenyl-25% methylpolysiloxane.
G18—Polyalkylene glycol.
G19—25% Phenyl-25% cyanopropyl-50% methylsilicone.
G20—Polyethylene glycol (av. mol. wt. of 380 to 420).
G21—Neopentyl glycol succinate.
G22—Bis(2-ethylhexyl) phthalate.
G23—Polyethylene glycol adipate.
G24—Diisodecyl phthalate.
G25—Polyethylene glycol compound TPA. A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with terephthalic acid. Available commercially as Carbowax 20M-TPA from suppliers of chromatographic reagents.
G26—25% 2-Cyanoethyl-75% methylpolysiloxane.
G27—5% Phenyl-95% methylpolysiloxane.
G28—25% Phenyl-75% methylpolysiloxane.
G29—3,3′-Thiodipropionitrile.
G30—Tetraethylene glycol dimethyl ether.
G31—Nonylphenoxypoly(ethyleneoxy)ethanol (av. ethyleneoxy chain length is 30); Nonoxynol 30.
G32—20% Phenylmethyl-80% dimethylpolysiloxane.
G33—20% Carborane-80% methylsilicone.
G34—Diethylene glycol succinate polyester stabilized with phosphoric acid.
G35—A high molecular weight compound of a polyethylene glycol and a diepoxide that is esterified with nitroterephthalic acid.
G36—1% Vinyl-5% phenylmethylpolysiloxane.
G37—Polyimide.
G38—Phase G1 containing a small percentage of a tailing inhibitor.[14]
G39—Polyethylene glycol (av. mol. wt. about 1500).
G40—Ethylene glycol adipate.
G41—Phenylmethyldimethylsilicone (10% phenyl-substituted).
G42—35% phenyl-65% dimethylpolysiloxane (percentages refer to molar substitution).
G43—6% cyanopropylphenyl-94% dimethylpolysiloxane (percentages refer to molar substitution).
G44—2% low molecular weight petrolatum hydrocarbon grease and 1% solution of potassium hydroxide.
G45—Divinylbenzene-ethylene glycol-dimethylacrylate.
G46—14% Cyanopropylphenyl-86% methylpolysiloxane.
G47—Polyethylene glycol (av. mol. wt. of about 8000).
G48—Highly polar, partially cross-linked cyanopolysiloxane.
~~G49—Proprietary derivatized phenyl groups on a polysiloxane backbone.[15]~~

■G~~50~~ ## (Docosahexaenoic Acid)—Polyethylene glycol, cross-linked (av. mol. wt. of more than 20,000).[g] ■1S (*USP27*)

[c] Available as Supelcosil ABZ from Supelco. (www.sigma-aldrich.com/supelco)

[d] Available as TSKgel G3000SW Column (analytical column) and TSKgel Guard (guard column) from Tosoh Biosep (part numbers 05103 and 05317, respectively). (www.tosohbiosep.com)

[14] A suitable grade is available commercially as "SP2100/0.1% Carbowax 1500" from Supelco, Inc., Supelco Park, Bellefonte, PA 16823.

~~[15] A suitable grade is available commercially as "Optima Delta-3" from Machery-Nagel, Inc., 215 River Vale Road, River Vale, NJ 07675.~~

[g] A suitable grade is available commercially as Famewax from Restek.

In-Process Revision

Supports

[NOTE—Unless otherwise specified, mesh sizes of 80 to 100 or, alternatively, 100 to 120 are intended.]

S1A—Siliceous earth for gas chromatography has been flux-calcined by mixing diatomite with Na_2CO_3 flux and calcining above 900°. The siliceous earth is acid-washed, then water-washed until neutral, but not base-washed. The siliceous earth may be silanized by treating with an agent such as dimethyldichlorosilane[16] to mask surface silanol groups.

S1AB—The siliceous earth as described above is both acid- and base-washed.[16]

S1C—A support prepared from crushed firebrick and calcined or burned with a clay binder above 900° with subsequent acid-wash. It may be silanized.

S1NS—The siliceous earth is untreated.

S2—Styrene-divinylbenzene copolymer having a nominal surface area of less than 50 m^2 per g and an average pore diameter of 0.3 to 0.4 μm.

S3—Copolymer of ethylvinylbenzene and divinylbenzene having a nominal surface area of 500 to 600 m^2 per g and an average pore diameter of 0.0075 μm.

S4—Styrene-divinylbenzene copolymer with aromatic –O and –N groups, having a nominal surface area of 400 to 600 m^2 per g and an average pore diameter of 0.0076 μm.

S5—40- to 60-mesh, high-molecular weight tetrafluorethylene polymer.

S6—Styrene-divinylbenzene copolymer having a nominal surface area of 250 to 350 m^2 per g and an average pore diameter of 0.0091 μm.

S7—Graphitized carbon having a nominal surface area of 12 m^2 per g.

S8—Copolymer of 4-vinyl-pyridine and styrene-divinylbenzene.

S9—A porous polymer based on 2,6-diphenyl-*p*-phenylene oxide.

S10—A highly polar cross-linked copolymer of acrylonitrite and divinylbenzene.

S11—Graphitized carbon having a nominal surface area of 100 m^2 per g modified with small amounts of petrolatum and polyethylene glycol compound.[17]

S12—Graphitized carbon having a nominal surface area of 100 m^2 per g.

BRIEFING

⟨**643**⟩ **Total Organic Carbon,** *USP 26* page 2139 and page 3156 of the *Second Supplement.* On the basis of comments received, the Pharmaceutical Waters Expert Committee has decided to cancel the previously proposed revisions (see page 1232 of *PF* 28(4) [July–Aug. 2002]) and is presenting this new proposal, which incorporates two methods that can be used to arrive at the TOC content: *Method 1* is the current qualitative pass/fail test, and *Method 2* is a quantitative test. Both analytical approaches provide equal assurance that the TOC limit is not exceeded. The Expert Committee encourages the submission of comments pertaining to this new proposal, which should be addressed to Frank Barletta, the liaison to the PW Expert Committee.

(PW: F. Barletta) RTS—39721-1

Change to read:

INTRODUCTION

Total organic carbon (TOC) is an indirect measure of organic molecules present in pharmaceutical waters measured as carbon. Organic molecules are introduced into the water from the source water, from purification and distribution system materials, and from biofilm growing in the system. TOC can also be used as a process control attribute to monitor the performance of unit operations comprising the purification and distribution system.

A number of acceptable methods exist for analyzing TOC. This chapter does not limit or prevent alternative technologies from being used, but provides guidance on how to qualify these analytical technologies for use as well as guidance on how to interpret instrument results for use as a limit test. The *Standard Solution* is a theoretically easy-to-oxidize solution that gives an instrument response at the attribute limit. The analytical technology is qualified by challenging the capability of the instrument using a theoretically difficult to oxidize solution in the system suitability portion of the method.

Analytical technologies utilized to measure TOC share the objective of completely oxidizing the organic molecules in an aliquot of sample water to carbon dioxide (CO_2), measuring the resultant CO_2 ~~levels,~~

■concentration,■2S (*USP27*)
and expressing this response as carbon concentration. All technologies must discriminate between the inorganic carbon, which may be present in the water from sources such as dissolved CO_2 and bicarbonate, and the CO_2 generated from the oxidation of organic molecules in the sample.

Two general approaches are used to measure TOC. One approach determines TOC by subtracting the measured inorganic carbon (IC) from the measured total carbon (TC), which is the sum of organic carbon and inorganic carbon:

$$TOC = TC - IC.$$

The other approach first purges the IC from the sample before any carbon measurement is performed. However, this IC purging step also purges some of the organic molecules, which can be retrapped, oxidized to CO_2, and quantitated as purgeable organic carbon (POC). The remaining organic matter in the sample is also oxidized to CO_2 and quantitated as nonpurgeable organic carbon (NPOC). In this approach, TOC is the sum of POC and NPOC:

$$TOC = POC + NPOC.$$

In pharmaceutical waters, the amount of POC is negligible,

■compared to the limit,■2S (*USP27*)
and can be discounted. Therefore, for the purpose of this methodology, NPOC is equivalent to TOC.

[16] Unless otherwise specified in the individual monograph, silanized support is intended.

[17] Commercially available as SP1500 on Carbopack B from Supelco.

In-Process Revision

Change to read:

REAGENT WATER

Use water having a TOC level of not more than 0.10 mg per liter. [NOTE—A conductivity requirement may be ~~necessary to ensure method reliability.~~

■specified by the equipment manufacturer.]■2S (*USP27*)

Change to read:

~~GLASSWARE~~

■CONTAINER■2S (*USP27*) PREPARATION

Organic contamination of ~~glassware~~

■containers■2S (*USP27*)
results in higher TOC values. Therefore, use ~~glassware and~~

▲▲*USP27*
sample containers that have been scrupulously cleaned of organic residues. Any method that is effective in removing organic matter can be used (see *Cleaning Glass Apparatus* ⟨1051⟩). Use *Reagent Water* for the final rinse.

Change to read:

TEST SOLUTION

NOTE—Use extreme caution when obtaining samples for TOC analysis. Water samples can be easily contaminated during the process of sampling and transportation to a testing facility.

Collect the *Test Solution* in ~~a tight container with minimal head space, and test in a timely manner to minimize the impact of organic contamination from the closure and container.~~

■such a manner that minimizes the impact of organic contamination.■2S (*USP27*)

Change to read:

SYSTEM SUITABILITY SOLUTION

~~Dissolve~~

■Unless otherwise directed in the monograph, dissolve■2S (*USP27*)
in *Reagent Water* an accurately weighed quantity of USP 1,4-Benzoquinone RS to obtain a solution having a concentration of ~~0.75 mg per liter (0.50 mg of carbon per liter).~~

■about 0.75 mg per liter (equal to 0.50 mg of carbon per liter).■2S (*USP27*)

Change to read:

REAGENT WATER CONTROL

Use a suitable quantity of *Reagent Water* obtained at the same time

■and in the same manner■2S (*USP27*)
as that used in the preparation of the *Standard Solution* and the *System Suitability Solution.*

Change to read:

OTHER CONTROL SOLUTIONS

Prepare appropriate reagent blank solutions or other specified solutions needed for establishing the apparatus baseline or for calibration adjustments following the manufacturer's instructions, and run the appropriate blanks to zero the instrument,

■if necessary.■2S (*USP27*)

Delete the following:

■~~SYSTEM SUITABILITY~~

~~Test the *Reagent Water Control* in the apparatus, and record the response, r_w. Repeat the test using the *Standard Solution,* and record the response, r_s. Calculate the corrected *Standard Solution* response, which is also the limit response, by subtracting the *Reagent Water Control* response from the response of the *Standard Solution.* The theoretical limit of 0.50 mg of carbon per liter is equal to the corrected *Standard Solution* response, $r_s - r_w$. Test the *System Suitability Solution* in the apparatus, and record the response, r_{ss}. Calculate the corrected *System Suitability Solution* response by subtracting the *Reagent Water Control* response from the response of the *System Suitability Solution*, $r_{ss} - r_w$. Calculate the response efficiency for the *System Suitability Solution* by the formula:~~

$$100[(r_{ss} - r_w)/(r_s - r_w)].$$

~~The system is suitable if the response efficiency is not less than 85% and not more than 115% of the theoretical response.~~■2S (*USP27*)

Delete the following:

■~~PROCEDURE~~

~~Perform the test on the *Test Solution,* and record the response, r_t. The *Test Solution* meets the requirements if r_t is not more than the limit response, $r_s - r_w$. This method also can be performed alternatively using on-line instrumentation that has been appropriately calibrated, standardized, and has demonstrated acceptable system suitability. The acceptability of such on-line instrumentation for quality attribute testing is dependent on its location(s) in the water system. These instrument location(s) and responses must reflect the quality of the water used.~~■2S (*USP27*)

In-Process Revision

Add the following:

▪METHOD SELECTION

Proceed using either *Method 1* or *Method 2,* as directed by the monograph. *Method 1* is a limit test that is designed for use as a test for the TOC attribute specifically for *Purified Water* and *Water for Injection*. *Method 2* is designed to be a more general test that could be used for many types of pharmaceutical waters, including *Purified Water* and *Water for Injection*. This method also accounts for small differences between the target solution concentrations and the actual solution concentrations in the system suitability testing. [NOTE—These methods can be performed using off-line or on-line instrumentation that has been appropriately calibrated and standardized, and that has demonstrated acceptable system suitability. The acceptability of such on-line instrumentation for quality attribute testing is dependent on its location(s) in the water system. These instrument location(s) and responses must reflect the quality of the water used.]

Method 1

System Suitability—At appropriate intervals based upon established instrument performance, test the *Reagent Water Control* in the apparatus, and record the response, r_W. Repeat the test using the *Standard Solution,* and record the response, r_S. Test the *System Suitability Solution* in the apparatus, and record the response, r_{SS}. Calculate the response efficiency for the *System Suitability Solution,* corrected for the reagent water, by the formula:

$$100[(r_{SS} - r_W)/(r_S - r_W)].$$

The system is suitable if the response efficiency is not less than 85% and not more than 115% of the theoretical response.

Procedure—Perform the test on the *Test Solution,* and record the response, r_U. The *Test Solution* meets the requirements if r_U is not more than the limit response, $r_S - r_W$.

Method 2

System Suitability—At appropriate intervals based upon established instrument performance, test the *Reagent Water Control* in the apparatus, and record the response, r_W. Repeat the test using the *Standard Solution,* and record the response, r_S. Test the *System Suitability Solution* in the apparatus, and record the response, r_{SS}. Calculate the response efficiency for the *System Suitability Solution,* corrected for the reagent water, by the formula:

$$63C_S(r_{SS} - r_W) / [C_{SS}(r_S - r_W)],$$

where C_S and C_{SS} are the concentrations of sucrose and 1,4-benzoquinone in the *Standard Solution* and *System Suitability Solution* (in mg per L), respectively. The system is suitable if the response efficiency is not less than 85% and not more 115%.

Procedure—Perform the test on the *Test Solution,* and record the response, r_U. Calculate the carbon concentration, C_C, of the *Test Solution* by the formula:

$$C_C = 0.42C_S r_U / (r_S - r_W),$$

where C_S is the concentration of sucrose in the *Standard Solution.* The *Test Solution* meets the requirements if C_C is not more than 0.50 mg per liter of carbon (500 ppb), unless otherwise directed in the monograph.▪2S (*USP27*)

In-Process Revision

BRIEFING

⟨**698**⟩ **Deliverable Volume,** *USP 26* page 2152. On the basis of comments received, it is proposed to revise this chapter in order to clarify the acceptance criteria. Decision schemes for multiple-unit containers and for single-unit containers are also added. Other editorial changes are included.

(PDF: H. Pappa) RTS—39877-1

Change to read:

The following tests are designed to provide assurance that oral ~~solutions and suspensions~~

■liquids■2S (*USP27*)
will, when transferred from the original container, deliver the volume of dosage form that is declared on the label of the article. These tests are applicable to products labeled to contain not more than 250 mL, whether supplied as liquid preparations or liquid preparations that are constituted from solids upon the addition of a designated volume of a specific diluent. They are not required for an article packaged in single-unit containers when the monograph includes the *Uniformity of Dosage Units* ⟨905⟩ test.

~~For the determination of deliverable volume, select not fewer than 30 containers, and proceed as follows for the dosage form designated.~~

~~ORAL SOLUTIONS, ORAL SUSPENSIONS, AND SYRUPS—Mix the contents of 10 containers individually.~~

~~POWDERS THAT ARE LABELED TO STATE THE VOLUME OF ORAL SOLUTION OR ORAL SUSPENSION THAT RESULTS WHEN THE POWDER IS CONSTITUTED WITH THE VOLUME OF DILUENT STATED IN THE LABELING—Constitute 10 containers with the volume of diluent stated in the labeling, accurately measured, and mix.~~

■■2S (*USP27*)

Add the following:

■TEST PREPARATIONS

For the determination of deliverable volume, select not fewer than 30 containers, and proceed as follows for the dosage form designated.

Oral Solutions, Oral Suspensions, and Other Oral Liquid Dosage Forms—Shake the contents of 10 containers individually.

Powders that are Labeled to State the Volume of Oral Liquid that Results when the Powder is Constituted with the Volume of Diluent Stated in the Labeling—Constitute 10 containers with the volume of diluent stated in the labeling, accurately measured, and shake individually.■2S (*USP27*)

Change to read:

PROCEDURE

~~Gently pour the contents of each container into a~~

■Being careful to avoid the formation of air bubbles, gently pour the contents of each container into■2S (*USP27*)
separate dry graduated cylinders of a rated capacity not exceeding two and a half times the volume to be measured, and calibrated "to

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contain". ~~being careful to avoid the formation of bubbles and allowing them~~

■Allow each container■2S (*USP27*) to drain for a period not to exceed 30 minutes, for multiple-unit containers and 5 seconds for single-unit containers, unless otherwise specified in the monograph. When free from air bubbles, measure the volume of each mixture. Alternatively, in the case of products of low volume packaged in single-unit containers, the volume can be computed ~~by discharging into a suitable tared container (allowing drainage for not more than 5 seconds), by determining the weight by difference and by computing the volume after determining the apparent density. The average volume of solution, suspension, or syrup obtained from the 10 containers is not less than 100%, and the volume of no container is less than 95%, and in the case of products packaged in single-unit containers, more than 110% of the volume declared in the labeling. If *A,* the average volume is less than 100% of that declared in the labeling, but the volume of no container is less than 95% of the labeled amount, or *B,* the volume of not more than 1 container is less than 95%, but is not less than 90% of the labeled volume, perform the test on 20 additional containers. The average volume of solution, suspension, or syrup obtained from the 30 containers is not less than 100% of the volume declared in the labeling; and the volume of solution, suspension, or syrup obtained from not more than 1 of the 30 containers is less than 95%, but not less than 90% of that declared in the labeling; and in the case of products packaged in single-unit containers, is more than 110%, but not more than 115% of that declared on the labeling.~~

■as follows: (1) discharge the container contents into a suitable tared container (allowing drainage for not more than 5 seconds); (2) determine the weight of the contents; and (3) compute the volume after determining the density.■2S (*USP27*)

Add the following:

■ACCEPTANCE CRITERIA

Use the following criteria to determine compliance with this test.

For Multiple-Unit Containers (see Figure 1)—The average volume of liquid obtained from the 10 containers is not less than 100%, and the volume of no container is less than 95% of the volume declared in the labeling. If *A,* the average volume is less than 100% of that declared in the labeling, but the volume of no container is less than 95% of the labeled amount, or *B,* the average volume is not less than 100% and the volume of not more than 1 container is less than 95%, but is not less than 90% of the labeled volume, perform the test on 20 additional containers. The average volume of liquid obtained from the 30 containers is not less than 100% of the volume declared in the labeling; and the volume of liquid obtained from not more than 1 of the 30 containers is less than 95%, but not less than 90% of that declared in the labeling.

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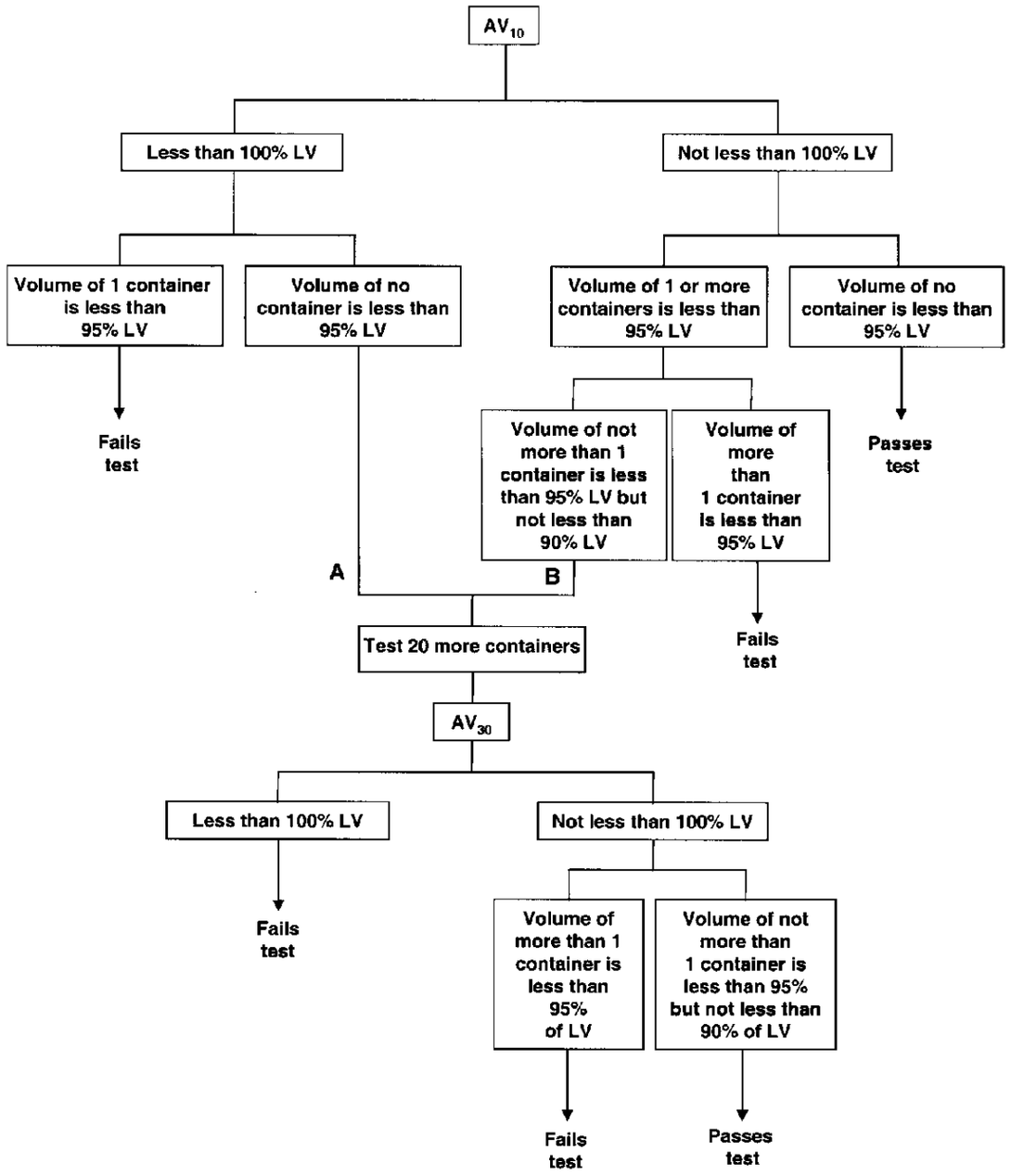

Figure 1. Decision scheme for multiple-unit containers. (AV = Average volume. LV = Labeled volume)

For Single-Unit Containers (see Figure 2)—The average volume of liquid obtained from the 10 containers is not less than 100%, and the volume of each of the 10 containers lies within the range of 95% to 110% of the volume declared in the labeling. If *A,* the average volume is less than 100% of that declared in the labeling, but the volume of no container is outside the range of 95% to 110%, or if *B,* the average volume is not less than 100% and the volume of not more than 1 container is outside the range of 95% to 110%, but within the range of 90% to 115%, perform the test on 20 additional containers. The average volume of liquid ob-

tained from the 30 containers is not less than 100% of the volume declared in the labeling; and the volume obtained from not more than 1 of the 30 containers is outside the range of 95% to 110%, but within the range of 90% to 115% of the volume declared on the labeling.

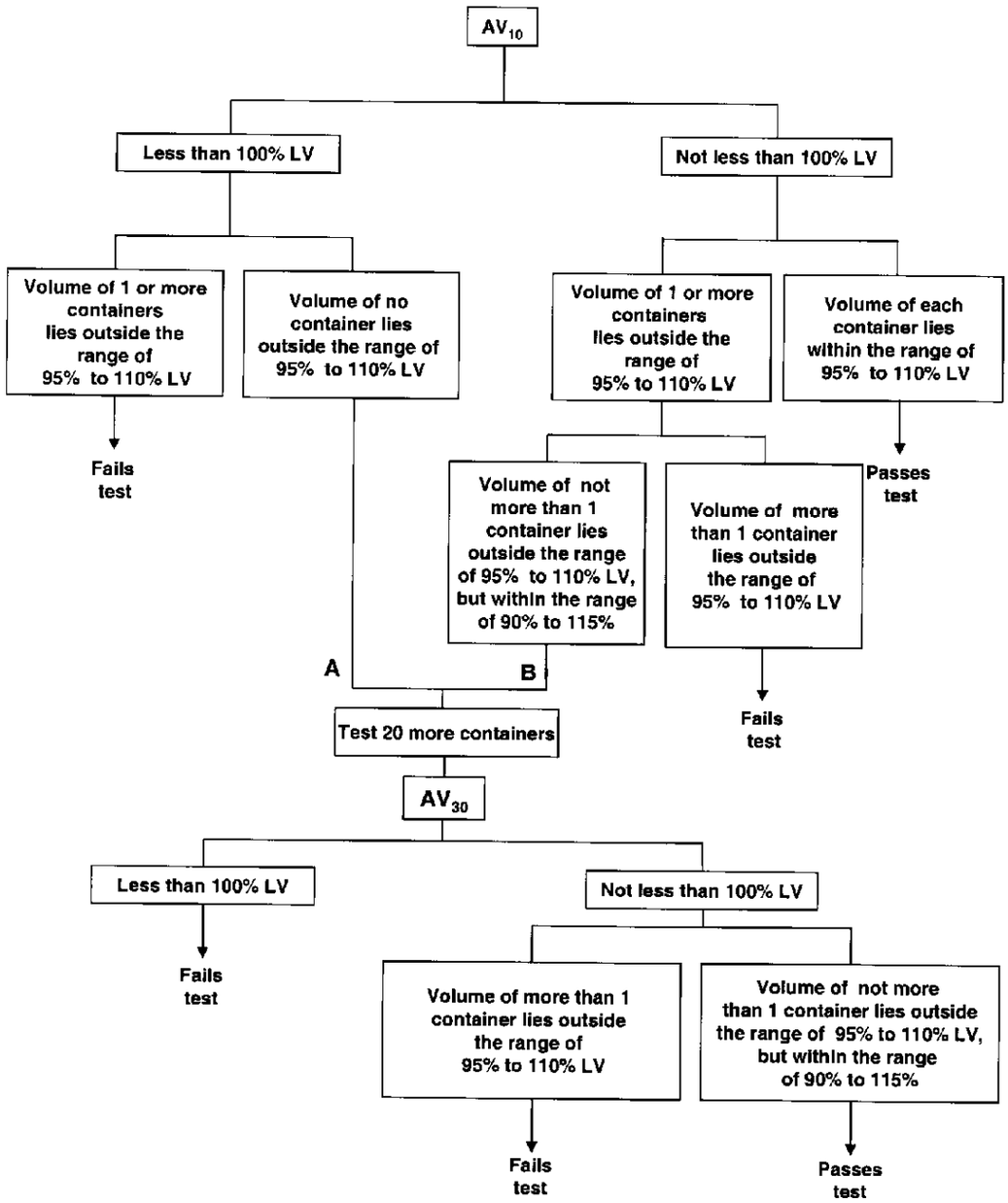

Figure 2. Decision scheme for single-unit containers. (AV = Average volume. LV = Labeled volume)

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BRIEFING

⟨**785**⟩ **Osmolarity,** *USP 26* page 2187. Several comments have been received regarding this chapter. The following proposal reflects those comments. A discussion evaluating the impact of this revision on monographs and general chapters that reference this chapter follows.

The official monographs of *Alcohol in Dextrose Injection* (*USP 26–NF 21,* p. 61) and *Iron Sucrose Injection* (*USP 26–NF 21,* pp. 1016–1017) require the label to state "the total osmolarity of the solution expressed in mOsmol per liter". There is no impact of the proposed chapter revision on these monographs because the proposed revision indicates that the osmolarity is expressed in mOsmol per liter unit.

The official monographs of *Ferumoxsil Oral Suspension* (*USP 26–NF 21,* p. 790), *Gadodiamide Injection* (*USP 26–NF 21,* pp.841–842), and *Iodixanol Injection* (*USP 26–NF 21,* pp. 994–995), and the proposed *In-Process Revision* of the monographs *Mangafodipir Trisodium Injection* (*PF* 29(4), pp. 1048–1049) and *Tobramycin Inhalation Solution* (*PF* 29(2), pp. 438–441) have a test for *Osmolarity* that refers to the general test chapter ⟨785⟩, but these monographs express the acceptance criteria for the test in mOsmol per kg unit, which is in fact the osmolality unit. In its present form, ⟨785⟩ may present the following problem for manufacturers. Because osmolarity cannot be measured experimentally, manufacturers may be measuring the osmolality of their products. However, there is no *USP* chapter that refers to osmolality, which means that manufacturers have no option but to call the test "osmolarity". The proposed revision will make it possible to state the test in terms of osmolality, thus eliminating the problem.

The monographs of *Manganese Chloride for Oral Solution* (*USP 26–NF 21,* p. 1124) and *PEG 3350 and Electrolytes for Oral Solution* (*USP 26–NF 21,* pp. 1493–1495) include a test for *Osmolarity* that refers to ⟨785⟩, but the acceptance criteria are expressed in mOsmol (without specifying "per liter" or "per kg").

The *Ferumoxides Injection* (*USP 26–NF 21,* pp. 788–790) monograph includes a test for *Osmolality,* with the acceptance criteria expressed in mOsmol per kg, but *Osmolarity* ⟨785⟩ is referenced.

The monographs *Aztreonam Injection* (*USP 26–NF 21,* p. 202) and *Cefoperazone Injection* (*USP 26–NF 21,* p. 367) mention "a suitable osmolality adjusting substance . . ." in the Definition sections. Because ⟨785⟩ does not include osmolality, the proposed revision in this *PF* will provide correct perspectives to the Definitions in these monographs.

In addition, appropriate revisions should be made to all of the above monographs, as necessary, to make the wording consistent with the Expert Committee's proposal in this *PF.*

The terms osmolarity and osmolality are also mentioned in USP chapters. The general test chapter *Radiopharmaceuticals for Positron Emission Tomography—Compounding* ⟨823⟩ (*USP 26–NF 21,* pp. 2213–2216) uses the term osmolality. Under *Background Information, for Ophthalmic Exposure* in the general information chapter *Excipient Biological Safety Evaluation Guidelines* ⟨1074⟩ (*USP 26–NF 21,* pp. 2320–2322) is the statement "define pH and osmolarity of topical ocular dose form". Also *Sterile Drug Products for Home Use* ⟨1206⟩ (*USP 26–NF 21,* pp. 2417–2429) mentions, " . . . and the critical product formulation parameters (pH, viscosity, ionic strength, and osmolarity) used to generate the supplied data . . .". However, none of the above chapters refer to ⟨785⟩. The proposed general test chapter *Pharmaceutical Compounding—Sterile Preparations* ⟨797⟩ [*PF* 28(2)] mentions osmolarity as a "critical product formulation parameter" but also does not refer to ⟨785⟩. On the other hand, the proposed general information chapter *Pharmaceutical Calculations in Prescription Compounding* ⟨1160⟩ [*PF* 29(1) p. 224–242] mentions osmolarity as a topic closely related to osmotic properties of solutions and does make reference to ⟨785⟩ as "see *Osmolarity* ⟨785⟩" and "See USP general chapters . . . *Osmolarity* ⟨785⟩". Clearly, the proposed revisions in this *PF* for *Osmolarity* ⟨785⟩ do not impact the above general chapters, except that in the proposed ⟨1160⟩ a revision will be necessary to change the title of the cross-reference from *Osmolarity* ⟨785⟩ to *Osmolality and Osmolarity* ⟨785⟩.

(PA4: H. Pappa) RTS—38159-1

Change to read:

⟨785⟩

■OSMOLALITY AND■2S (*USP27*)
OSMOLARITY

~~Osmotic pressure is fundamentally related to all biological processes that involve diffusion of solutes or transfer of fluids through membranes. Thus, knowledge of the osmolar concentrations of parenteral fluids is essential. The labels of Pharmacopeial solutions that provide intravenous replenishment of fluid, nutrient(s), or electrolyte(s), as well as of the osmotic diuretic Mannitol Injection, are required to state the osmolar concentration.~~

~~The declaration of osmolar concentration on the label of a parenteral solution serves primarily to inform the practitioner whether the solution is hypo-osmotic, iso-osmotic, or hyper-osmotic. A quantitative statement facilitates calculation of the dilution required to render a hyper-osmotic solution iso-osmotic. It also simplifies many calculations involved in peritoneal dialysis and hemodialysis procedures. The osmolar concentration of an extemporaneously compounded intravenous solution prepared in the pharmacy (e.g., a hyperalimentation solution) from osmolar labeled solutions also can be obtained simply by summing the osmoles contributed by each constituent.~~

~~The units of osmolar concentration are usually expressed as milliosmoles (abbreviation: mOsmol) of solute per liter of solution. In general terms, the weight of an osmole is the gram molecular weight of a substance divided by the number of ions or chemical species *(n)* formed upon dissolution. In ideal solutions, for example, n = 1 for glucose, n = 2 for sodium chloride or magnesium sulfate, n = 3 for calcium chloride, and n = 4 for sodium citrate.~~

~~The ideal osmolar concentration may be determined according to the formula:~~

~~osmolar concentration (mOsmol / liter) = mOsM~~

$$= \frac{\text{wt. of substance (g/liter)}}{\text{mol. wt. (g)}} \times \text{number of species} \times 1000.$$

~~As the concentration of the solute increases, interaction among solute particles increases, and actual osmolar values decrease when compared to ideal values. Deviation from ideal conditions is usually slight in solutions within the physiologic range and for more dilute solutions, but for highly concentrated solutions the actual osmolarities may be appreciably lower than ideal values. For example, the ideal osmolarity of 0.9% Sodium Chloride Injection is 9/58.4 × 2 × 1000 = 308 milliosmoles per liter. In fact, however, n is slightly less than 2 for solutions of sodium chloride at this concentration, and the actual measured osmolarity of 0.9% Sodium Chloride Injection is about 286 milliosmoles per liter.~~

~~The theoretical osmolarity of a complex mixture, such as Protein Hydrolysate Injection, cannot be readily calculated. In such instances, actual values of osmolar concentration are to be used to meet the labeling requirement set forth in the individual mono-~~

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~~graph. They are determined by calculating the osmolarity from measured values of osmolal concentration and water content. Each osmole of solute added to 1 kg of water lowers the freezing point approximately 1.86° and lowers the vapor pressure approximately 0.3 mm of mercury (at 25°). These physical changes are measurable, and they permit accurate estimations of osmolal concentrations.~~

~~Where osmometers that measure the freezing point depression are employed, a measured volume of solution (usually 2 mL) is placed in a glass tube immersed in a temperature-controlled bath. A thermistor and a vibrator are lowered into the mixture, and the temperature of the bath is decreased until the mixture is supercooled. The vibrator is activated to induce crystallization of the water in the test solution, and the released heat of fusion raises the temperature of the mixture to its freezing point. By means of a Wheatstone bridge, the recorded freezing point is converted to a measurement in terms of milliosmolality, or its near equivalent for dilute solutions, milliosmolarity. The instrument is calibrated by using two standard solutions of sodium chloride that span the expected range of osmolarities.~~

~~Osmometers that measure the vapor pressures of solutions are less frequently employed. They require a smaller volume of specimen (generally about 5 µL), but the accuracy and precision of the resulting osmolality determination are comparable to those obtained by the use of osmometers that depend upon the observed freezing points of solutions.~~

~~**Labeling**—Where an osmolarity declaration is required in the individual monograph, the label states the total osmolar concentration in milliosmoles per liter. Where the contents are less than 100 mL, or where the label states that the article is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolar concentration in milliosmoles per milliliter.~~

▪INTRODUCTION

Osmotic pressure plays a critical role in all biological processes that involve diffusion of solutes or transfer of fluids through membranes. Osmosis occurs when solvent but not solute molecules cross a semipermeable membrane from regions of lower to higher concentrations to produce equilibrium. The knowledge of osmotic pressures is important for practitioners in determining whether a parenteral solution is hypo-osmotic, iso-osmotic, or hyperosmotic. A quantitative measure of osmotic pressure facilitates the dilution required to render a solution iso-osmotic relative to whole blood.

OSMOTIC PRESSURE

The osmotic pressure of a solution depends on the number of particles in solution, and is therefore referred to as a colligative property. A particle can be a molecule or an ion or an aggregated species (e.g., a dimer) that can exist discretely in solution. A solution exhibits ideal behavior when no interaction occurs between solutes and solvent, except where solvent molecules are bound to solutes by hydrogen bonding or coordinate covalency. For such a solution containing a nondissociating solute, the osmotic pressure (π) is directly proportional to its molality (number of moles of solute per kilogram of the solvent):

$$\pi = (\rho RT/1000)m,$$

where ρ is the density of the solvent at the temperature T (in the absolute scale); R is the universal gas constant; and m is the molality of the solution. For a real solution containing more than one solute, the osmotic pressure is given by the formula:

$$\pi = (\rho RT/1000)\Sigma\nu_i m_i \Phi_{m,i},$$

where ν_i is the number of particles formed by the dissociation of one molecule of the i^{th} solute, $\nu_i = 1$ for nonionic (nondissociating) solutes, m_i is the molality of the i^{th} solute, and $\Phi_{m,i}$ is the molal osmotic coefficient of the i^{th} solute. The molal osmotic coefficient takes into account the deviation of a solution from ideal behavior. Its value depends upon the concentration of the solute(s) in solution, its chemical properties, and ionic characteristics. The value of the molal osmotic coefficient of a solute can be determined experimentally by measuring the freezing point depression

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at different molal concentrations. At concentrations of pharmaceutical interest, the value of the molal osmotic coefficient is less than one. The molal osmotic coefficient decreases with the increase in concentration of the solute (*Table 1*).

OSMOLALITY

The osmolality of a solution ξ_m is given by

$$\xi_m = \Sigma \nu_i m_i \Phi_{m,i},$$

The osmolality of a real solution corresponds to the molality of an ideal solution containing nondissociating solutes and is expressed in osmoles or milliosmoles per kilogram of solvent (Osm per kg or mOsm per kg, respectively), a unit that is similar to the molality of the solution. Thus, osmolality is a measure of the osmotic pressure exerted by a real solution across a semipermeable membrane. Like osmotic pressure, other colligative properties of a solution, such as vapor pressure lowering, boiling point elevation, and freezing point depression, are also directly related to the osmolality of the solution. Indeed, the osmolality of a solution is typically determined most accurately and conveniently by measuring freezing point depression (ΔT_f):

$$\Delta T_f = k_f \xi_m,$$

where, k_f is the molal cryoscopic constant, which is a property of the solvent. For water, the value of k_f is 1.860° per osmole. That is, 1 osmole of a solute added to 1 kg of water lowers the freezing point by 1.860°.

OSMOLARITY

Osmolarity of a solution is a theoretical quantity expressed in osmoles per liter of a solution and is widely used in clinical practice because it expresses osmoles as a function of volume. Osmolarity cannot be measured but is calculated theoretically from the experimentally measured value of osmolality.

Sometimes, osmolarity (ξ_c) is calculated theoretically from the molar concentrations:

$$\xi_c = \Sigma \nu_i c_i,$$

where ν_i is as defined above, and c_i is the molar concentration of the i^{th} solute in solution. For example, the osmolarity of a solution prepared by dissolving 1 g of vancomycin in 100 mL of 0.9% sodium chloride solution can be calculated as follows:

[3 × 10 g/L/1468 (mol. wt. of vancomycin) + 2 × 9 g/L/58.5 (mol. wt. of sodium chloride)] × 1000 = 328mOsm/L.

The results suggest that the solution is slightly hyperosmotic since the osmolaltiy of blood ranges between 285 and 310 mOsm per kg. However, the solution is found to be hypo-osmotic and has an experimentally determined osmolality of 255 mOsm per kg.[1] The example illustrates that osmolarity values calculated theoretically from the concentration of a solution should be interpreted cautiously and may not represent the osmotic properties of infusion solutions.

The discrepancy between theoretical (osmolarity) and experimental (osmolality) results is, in part, due to the fact that osmotic pressure is related to osmolality and not osmolarity. More significantly, the discrepancy between experimental results and the theoretical calculation is due to the fact that the osmotic pressure of a real solution is less than that of an ideal solution because of interactions between solute molecules or between solute and solvent molecules in a solution. Such interactions reduce the pressure exerted by solute molecules on a semipermeable membrane, reducing experimental values of osmolality compared to theoretical

[1] Kastango, E.S. and Hadaway, L. (2001) *International Journal of Pharmaceutical Compounding 5,* 465-469.

values. This difference is related to the molal osmotic coefficient ($\Phi_{m,i}$). The example also illustrates the importance of determining the osmolality of a solution experimentally, rather than calculating the value theoretically.

MEASUREMENT OF OSMOLALITY

The osmolality of a solution is commonly determined by the measurement of the freezing point depression of the solution.

Apparatus—The apparatus, an osmometer for freezing point depression measurement, consists of the following: a means of cooling the container used for the measurement; a resistor sensitive to temperature (thermistor), with an appropriate current- or potential-difference measurement device that may be graduated in temperature change or in osmolality; and a means of mixing the sample.

Standard Solutions—Prepare *Standard Solutions* as specified in *Table 1*, as necessary.

Table 1. Standard Solutions for Osmometer Calibration[2]

Standard Solutions (Weight in g of sodium chloride per kg of water)	Osmolality (mOsm/kg) (ξ_m)	Molal Osmotic Coefficient ($\Phi_{m,\ NaCl}$)	Freezing Point Depression (°) ΔT_f
3.087	100	0.9463	0.186
6.260	200	0.9337	0.372
9.463	300	0.9264	0.558
12.684	400	0.9215	0.744
15.916	500	0.9180	0.930
19.147	600	0.9157	1.116
22.380	700	0.9140	1.302

[2] Adapted from the *European Pharmacopoeia,* 4th Edition, 2002, p. 50.

Test Solution—For a solid for injection, constitute with the appropriate diluent as specified in the instructions on the labeling. For solutions, use the sample as is. [NOTE—A solution can be diluted to bring it within the range of measurement of the osmometer, if necessary, but the results must be expressed as that of the diluted solution and must NOT be multiplied by a dilution factor to calculate the osmolality of the original solution. The molal osmotic coefficient is a function of concentration. Therefore, it changes with dilution.]

Procedure—Set the zero of the apparatus using water. To calibrate the apparatus, choose at least two solutions from *Table 1* such that the osmolalities of the *Standard Solutions* span the expected range of osmolality of the *Test Solution.* Introduce an appropriate volume of each *Standard Solution* into the measurement cell as per the manufacturer's instructions, and start the cooling system. Usually, the mixing device is programmed to operate at a temperature below the lowest temperature expected from the freezing point depression. The apparatus indicates when the equilibrium is attained. Calibrate the osmometer using an appropriate

adjustment device such that the reading corresponds to either the osmolality or freezing point depression value of the *Standard Solution* shown in *Table 1.* [NOTE—Some instruments indicate osmolality and some others show freezing point depression.] Before each measurement, rinse the measurement cell at least twice with the solution to be tested. Repeat the procedure with each *Test Solution.* Read the osmolality of the *Test Solution* directly, or calculate it from the measured freezing point depression.

Assuming that the value of the osmotic coefficient is essentially the same whether the concentration is expressed in molality or molarity, the experimentally determined osmolality of a solution can be converted to osmolarity in the same manner in which the concentration of a solution is converted from molality to molarity. Unless a solution is very concentrated, the osmolarity of a solution (ξ_c) can be calculated from its experimentally determined osmolality (ξ_m):

$$\xi_c = 1000\xi_m / (1000 / \rho + \Sigma w_i \nu_i),$$

where w_i, is the weight in g; and ν_i is the partial specific volume, in mL per g, of the i^{th} solute. The partial specific volume of a solute is the change in volume of a solution when an additional 1 g of solute is dissolved in the solution. This volume can be determined by the measurement of densities of the solution before and after the addition of the solute. The partial specific volumes of salts are generally very small, around 0.1 mL per g. However, those of other solutes are generally higher. For example, the partial specific volumes of amino acids are in the range of 0.6–0.9 mL per g.■2S (*USP27*)

BRIEFING

⟨**791**⟩ **pH,** *USP 26* page 2196. It is proposed to revise under *Buffer Solutions for Standardization of the pH Meter* the type of storage containers used and the accuracy for standardization solutions with a pH of 4 or lower. Editorial style changes are also made.

(PA4: H. Pappa) RTS—38500-1

Change to read:

For compendial purposes, pH is defined as the value given by a suitable, properly standardized, potentiometric instrument (pH meter) capable of reproducing pH values to 0.02 pH unit using an indicator electrode sensitive to hydrogen-ion activity, the glass electrode, and a suitable reference electrode. The instrument should be capable of sensing the potential across the electrode pair and, for pH standardization purposes, applying an adjustable potential to the circuit by manipulation of "standardization," "zero," "asymmetry," or "calibration" control, and should be able to control the change in millivolts per unit change in pH reading through a "temperature" and/or "slope" control. Measurements are made at 25 ± 2°, unless otherwise specified in the individual monograph or herein.

The pH scale is defined by the equation:

$$\text{pH} = \text{pHs} + (E - E_S) / k,$$

in which E and E_S are the measured potentials where the galvanic cell contains the solution under test, represented by pH, and the appropriate *Buffer Solution for Standardization,* represented by pHs, respectively. The value of k is the change in potential per unit change in pH and is theoretically $[0.05916 + 0.000198(t - 25°)]$ volts at any temperature t. ~~This operational pH scale is established by assigning rounded pH values to the *Buffer Solutions for Standardization* from the corresponding National Institute of Standards and Technology *molal* solutions.~~

■■2S (*USP27*)
It should be emphasized that the definitions of pH, the pH scale, and the values assigned to the *Buffer Solutions for Standardization* are for the purpose of establishing a practical, operational system so that results may be compared between laboratories. The pH values thus measured do not correspond exactly to those obtained by the definition, $\text{pH} = -\log a_{H^+}$. So long as the solution being measured is sufficiently similar in composition to the buffer used for standardization, the operational pH corresponds fairly closely to the theoretical pH. Although no claim is made with respect to the suitability of the system for measuring hydrogen-ion activity or concentration, the values obtained are closely related to the activity of the hydrogen ion in aqueous solutions.

Where a pH meter is standardized by use of an aqueous buffer and then used to measure the "pH" of a nonaqueous solution or suspension, the ionization constant of the acid or base, the dielectric constant of the medium, the liquid-junction potential (which may give rise to errors of approximately 1 pH unit), and the hydrogen-ion response of the glass electrode are all changed. For these reasons, the values so obtained with solutions that are only partially aqueous in character can be regarded only as apparent pH values.

Change to read:

BUFFER SOLUTIONS FOR STANDARDIZATION OF THE PH METER

Buffer Solutions for Standardization are to be prepared as directed in the *accompanying table*.* Buffer salts of requisite purity can be obtained from the National Institute of Science and Technology. Solutions may be stored in ~~chemically resistant, tight containers, such as Type I glass bottles. Fresh solutions should be prepared at intervals not to exceed 3 months.~~ ■hard glass or polyethylene bottles fitted with a tight closure or carbon dioxide-absorbing tube (soda lime). Fresh solutions should be prepared at intervals not to exceed 3 months using carbon dioxide-free water.■2S (*USP27*)

The table indicates the pH of the buffer solutions as a function of temperature. The instructions presented here are for the preparation of solutions having the designated molal *(m)* concentrations. For convenience, and to facilitate their preparation, however, instructions are given in terms of dilution to a 1000-mL volume rather than specifying the use of 1000 g of solvent, which is the basis of the molality system of solution concentration. The indicated quantities cannot be computed simply without additional information.

pH Values of Buffer Solutions for Standardization

Temperature, °C	Potassium Tetraoxalate, 0.05 *m*	Potassium Biphthalate, 0.05 *m*	Equimolal Phosphate, 0.05 *m*	Sodium Tetraborate, 0.01 *m*	Calcium Hydroxide, Saturated at 25°
10	1.67	4.00	6.92	9.33	13.00
15	1.67	4.00	6.90	9.28	12.81
20	1.68	4.00	6.88	9.23	12.63
25	1.68	4.01	6.86	9.18	12.45
30	1.68	4.02	6.85	9.14	12.29
35	1.69	4.02	6.84	9.10	12.13
40	1.69	4.04	6.84	9.07	11.98
45	1.70	4.05	6.83	9.04	11.84
50	1.71	4.06	6.83	9.01	11.71
55	1.72	4.08	6.83	8.99	11.57
60	1.72	4.09	6.84	8.96	11.45

Potassium Tetraoxalate, 0.05 m—Dissolve 12.61 g of $KH_3(C_2O_4)_2 \cdot 2H_2O$ in water to make 1000 mL.

Potassium Biphthalate, 0.05 m—Dissolve 10.12 g of $KHC_8H_4O_4$, previously dried at 110° for 1 hour, in water to make 1000 mL.

Equimolal Phosphate, 0.05 m—Dissolve 3.53 g of Na_2HPO_4 and 3.39 g of KH_2PO_4, each previously dried at 120° for 2 hours, in water to make 1000 mL.

Sodium Tetraborate, 0.01 m—Dissolve 3.80 g of $Na_2B_4O_7 \cdot 10H_2O$ in water to make 1000 mL. Protect from absorption of carbon dioxide.

Calcium Hydroxide, saturated at 25°—Shake an excess of calcium hydroxide with water, and decant at 25° before use. Protect from absorption of carbon dioxide.

Because of variations in the nature and operation of the available pH meters, it is not practicable to give universally applicable directions for the potentiometric determinations of pH. The general principles to be followed in carrying out the instructions provided for each instrument by its manufacturer are set forth in the following paragraphs. Examine the electrodes and, if present, the salt bridge prior to use. If necessary, replenish the salt bridge solution, and observe other precautions indicated by the instrument or electrode manufacturer.

To standardize the pH meter, select two *Buffer Solutions for Standardization* whose difference in pH does not exceed 4 units and such that the expected pH of the material under test falls between them. Fill the cell with one of the *Buffer Solutions for Standardization* at the temperature at which the test material is to be measured. Set the "temperature" control at the temperature of the solution, and adjust the calibration control to make the observed pH value identical with that tabulated. Rinse the electrodes and cell with several portions of the second *Buffer Solution for Standardization,* then fill the cell with it, at the same temperature as the material to be measured. The pH of the second buffer solution is within ±0.07 pH unit of the tabulated value. If a larger deviation is noted, examine the electrodes and, if they are faulty, replace them. Adjust the "slope" or "temperature" control to make the observed pH value identical with that tabulated. Repeat the standardization until both *Buffer Solutions for Standardization* give observed pH values within 0.02 pH unit of the tabulated value without further adjustment of the controls. When the system is functioning satisfactorily, rinse the electrodes and cell several times with a few portions of the test material, fill the cell with the test material, and read the pH value. Use carbon dioxide-free water (see *Water* in the section *Reagents, Indicators, and Solutions*) for solution or dilution of test material in pH determinations. In all pH measurements, allow a sufficient time for stabilization.

Where approximate pH values suffice, indicators and test papers (see *Indicators and Indicator Test Papers,* in the section *Reagents, Indicators, and Solutions*) may be suitable.

For a discussion of buffers, and for the composition of standard buffer solutions called for in compendial tests and assays, see *Buffer Solutions* in the section *Reagents, Indicators, and Solutions.*

* Commercially available buffer solutions for pH meter standardization, standardized by methods traceable to the National Institute of Standards and Technology (NIST), labeled with a pH value accurate to 0.01 pH unit may be used.

■For standardization solutions having a pH lower than 4, a labeled accuracy of 0.02 is acceptable.■2S (*USP27*)

Solutions prepared from ACS reagent grade materials or other suitable materials, in the stated quantities, may be used provided the pH of the resultant solution is the same as that of the solution prepared from the NIST certified material.

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GENERAL CHAPTERS

General Information

BRIEFING

General Information Chapters, *USP 26* page 2235. The proposed revision to the introduction to the General Information Chapters is intended to allow the use, where specified in individual monographs, of chapters having a number greater than 1000.

(DSN: T. Cecil) RTS—40437-2

Change to read:

The chapters in this section are information, and aside from excerpts given herein from Federal Acts and regulations that may be applicable, they contain no standards, tests, assays, nor other mandatory specifications, with respect to any Pharmacopeial articles,

■unless specifically referenced in a monograph or elsewhere

in this *Pharmacopeia.*■2S (*USP27*)
The excerpts from pertinent Federal Acts and regulations included in this section are placed here inasmuch as they are not of Pharmacopeial authorship. Revisions of the federal requirements that affect these excerpts will be included in *USP Supplements* as promptly as practical. The official requirements for Pharmacopeial articles are set forth in the *General Notices,* the individual monographs, and the *General Tests and Assays* chapters of this *Pharmacopeia.*

BRIEFING

⟨1119⟩ Near-Infrared Spectrophotometry, *USP 26* page 2388 and page 735 of *PF* 29(3) [May–June 2003]. On the basis of comments received, this general information chapter is being revised to increase consistency with the *Glossary* and to refine and clarify the chapter. The formula for RMS noise has also been corrected.

(PA6: G. Ritchie) RTS—39707-1; 39823-1; 39846-1; 40002-1; 40064-1; 40264-1; 40265-1; 40269-1

Change to read:

INTRODUCTION

~~Near-IR (NIR) spectroscopy is a specialized branch of spectroscopy and shares many of the attributes of other spectroscopic measurements discussed in *Spectrophotometry and Light-Scattering* ⟨851⟩. The NIR spectral region includes two subranges, each requiring a specific detector. For the short-wavelength IR, or Herschel range, that extends from 700 to 1100 nm, silicon-based photodetectors are suitable for measurements. Lower energies and longer wavelengths between 1100 and 2500 nm comprise the NIR subregion in which lead sulfide (PbS) or indium-gallium-arsenide (InGaAs) detectors are used. [NOTE—See the final section of this chapter, *Definition of Terms and Symbols*, for the terms and symbols referred to in this chapter and commonly employed in NIR spectroscopy.]~~

~~NIR spectroscopy is advantageous because quick and accurate measurements can often be made without destroying the sample. Molecular spectra in this region are dominated by overtones and combinations of fundamental vibrational modes, which are much weaker than the fundamental vibrations encountered in the mid-IR region. Because there is much less light absorption in the NIR range, radiation typically penetrates several millimeters into materials, including solids. Furthermore, many materials such as glass are relatively transparent in this region, so the optics in NIR spectrometers are comparatively robust and inexpensive. Fiber optic technology is readily implemented in the NIR range, which allows remote monitoring of processes in challenging environments.~~

~~Transmittance and Reflectance~~

~~Two different measurements commonly performed in the NIR spectral range are transmittance and reflectance.~~

~~TRANSMITTANCE, or direct sample absorption, measures the decrease in radiation intensity as a function of wavelength when radiation is passed through the sample. The sample, which must be relatively transparent to the radiation, is placed in the optical beam path between the source and the detector. This arrangement is analogous to that in many conventional spectrophotometers, and the results can be presented directly in terms of absorbance (see *Definition of Terms and Symbols*). Because tungsten filament lamp sources can be highly stabilized, many NIR instruments have the single-beam design. The intensity of the source radiation, I_o, is scanned and stored. Samples are then scanned, and their absorbances are calculated with the aid of the stored data. A variation of this technique called transflectance places a reflector behind the sample to double the path length. This configuration can be adapted to share the same instrument geometry with reflectance or fiber-optic probe systems where the source and the detector are on the same side of the sample.~~

~~REFLECTANCE, or diffuse reflectance, r, measures the ratio of the intensity of light reflected from the sample, I, to that reflected from a background or reference reflective surface, I_o (see *Definition of Terms and Symbols*). For these measurements, I_o, determined from a standard reflector, is an approximation of the energy incident on the sample surface. NIR radiation penetrates a substantial distance (1 to 3 mm) into the sample, where it can be absorbed by the vibrational combinations and overtones from the analyte species present in the sample. Unabsorbed radiation is reflected back from the sample. A plot of reflectance, as a function of wavelength in the NIR region, exhibits bands of low reflectance where light absorption has occurred. In many instances, these spectral bands adhere to Beer's law with respect to concentration of components in the mixture. [NOTE—Beer's law may not hold for all solid mixtures in NIR~~

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reflectance. However, if calibration curves are established, quantitative work can be performed.] NIR reflectance spectra are typically treated in the same way as conventional absorption spectra, by calculating and plotting $\log(1/r)$ versus wavelength. In analogy to conventional transmittance spectrophotometry, this logarithmic form is commonly called "absorbance". However, the background spectrum (see *Definition of Terms and Symbols*) may differ substantially from the sample spectrum. Thus, artifacts, such as nonlinear bands, negative absorbances, or areas where the absorbance exceeds the dynamic range of the instrument, may appear.

Most NIR reflectance spectra are collected from samples such as powders or compressed heterogeneous solids such as whole tablets. Solids typically exhibit a broad upward slope in absorbance toward longer wavelengths. Variations in particle size, shape, compaction, and other physical differences between samples can cause shifts in spectral baselines and hence interfere with quantitation. Mathematical techniques are available to reduce or eliminate particle size dependence, if deemed necessary. The most common procedure is to take the first or second derivative of the spectrum. Derivatives are practical in the NIR region because of the low noise and high photometric precision. Where data are available on large numbers of nearly identical samples, multiplicative scatter correction (MSC) is an alternative to taking derivatives. The corrected absorbance spectra may then be used directly for quantitation. In pharmaceutical analysis, particle size information may be pertinent to the safety and effectiveness of the product. Thus, techniques aimed at eliminating particle size effects in NIR reflectance are applied on a case-by-case basis.

Other Factors Affecting Quantitation

Sample Temperature— This parameter is most important for solutions, especially aqueous solutions, where a difference of a few degrees can result in substantial changes. It appears to be less critical for solids in NIR reflectance but may need to be considered for accurate work. If sample temperature cannot be controlled, then it should be measured and recorded. These data can then be used to determine whether sample temperature affects the results, and if it does, then sample temperature data provide a basis upon which a suitable correction for temperature effects can be formulated. Various methods exist to calculate the appropriate temperature correction.

Moisture and Residual Solvents— Adsorbed moisture, which is nonchemically bound, and water of hydration contribute to bands in the NIR region. NIR methods for moisture determination have been developed. It is important to maintain consistent room humidity for samples affected by humidity variations. This problem may be avoided if samples are kept in, and measured directly through, sealed containers. Other residual solvents may also contribute to the spectrum.

Sample Thickness— Because NIR radiation is absorbed much less than mid-IR radiation, the light can penetrate several millimeters into the sample. It is important to use methods that ensure a consistent light path. To achieve this, the sample must be "infinitely" thick, or thinner samples of constant thickness must have a stable, diffusely reflecting backing material of constant, and preferably high, reflectivity. In measurements of reflectance, it is desirable to use samples that are optically infinitely thick at all wavelengths. That is, measurements of samples of various depths should demonstrate that their spectra do not change for sample depths greater than the chosen measurement depth. Where transmittance or transflectance of intact samples is possible, steps are taken to ensure that all method calibration standards and analytical samples are of the same optical thickness or reflected path length. For liquid samples, the same or a matching cell is used for backgrounds, references, and samples.

Sample Optical Properties— In solids, both surface and bulk scattering properties of calibration standards and analytical samples must be taken into account. Spectra of physically, chemically, or optically heterogeneous samples may require sample averaging by increasing the beam size or examining multiple samples. Certain factors, such as the differing degrees of sample compaction in powdered materials, can cause significant spectral differences. Glossiness of the surface finish of samples (e.g., coated tablets) may add a specular reflectance component to the observed NIR reflectance. Specular reflectance can distort the diffuse reflectance absorption peaks and may thereby interfere with quantitation.

Polymorphism— Because NIR reflectance can be measured directly for solid crystalline substances, variations in crystalline structure (polymorphism) influence the spectra. Hence, polymorphs as well as the amorphous solids may be distinguished from one another on the basis of their NIR spectra. Where multiple polymorphs can coexist in an otherwise chemically pure bulk drug substance, care must be taken to ensure that the calibration standards have a distribution of polymorphs matching that of the test specimen.

Age of Samples— Some samples may change their chemical, physical, or optical properties over time. Care must be taken to ensure that samples for NIR analysis are representative of those used for calibration. If samples of different age are to be analyzed, potential differences in properties must be accounted for in the calibration sample set.

■Near-infrared (NIR) spectroscopy is a branch of spectroscopy that shares many of the principles that apply to other spectroscopic measurements discussed in *Spectrophotometry and Light-Scattering* ⟨851⟩. The NIR spectral region includes two subranges. The short-wavelength or Herschel range extends from approximately 780 750 to 1100 nm, (~12,800–9000 cm^{-1}), (~13,333–9000 cm^{-1}), while longer wavelengths between 1100–2500 nm (~9,000–4000 cm^{-1}) comprise the traditional NIR region. In common with other spectrophotometric measurements, NIR is used for both qualitative and quantitative assessment of the chemical composition of samples. It may also be sensitive to physical properties of the sample. Measurements can be made directly on in-situ samples, in addition to standard sampling and testing procedures. Typical applications of NIR spectra utilize both wavelength and wavenumber units.

Vibrational spectroscopy in the NIR region is dominated by overtones and combinations that are much weaker than the fundamental mid-IR vibrations from which they originate. Because molar absorptivities in the NIR range are low, radiation typically penetrates several millimeters into materials, including solids. Furthermore, many materials

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such as glass are relatively transparent in this region. Fiber-optic technology is readily implemented in the NIR range, which allows monitoring of processes in inaccessible, remote, and challenging environments.

The tests and criteria given in this chapter may not be appropriate for all instrument configurations, particularly on-line process analytical technology measurements. In such cases, alternative instrument qualification and performance checks should be scientifically justified.

Transmittance and Reflectance

Two different measurements commonly performed in the NIR spectral range are transmittance and reflectance.

TRANSMITTANCE, *T*, measures the decrease in radiation intensity as a function of wavelength when radiation is passed through the sample. The sample is placed in the optical beam between the source and the detector. This arrangement is ~~analogous to that in~~ similar to many conventional spectrophotometers, and the results can be presented directly in terms of absorbance. A variation of this technique, transflectance, places a reflector behind the sample so as to double the path length. This configuration can be adapted to share the same instrument geometry with reflectance or fiber-optic probe systems where the source and the detector are on the same side of the sample.

REFLECTANCE, *R*, measures the ratio of the intensity of light reflected from the sample, *I*, to that reflected from a background or reference reflective surface, I_r, NIR radiation can penetrate a substantial distance into the sample, where it can be absorbed by the vibrational combinations and overtones of the analyte species present in the sample. Nonabsorbed radiation is reflected back from the sample to the detector. NIR reflectance spectra are accessed by calculating and plotting $\log(1/R)$ versus wavelength. This logarithmic form is commonly called absorbance.

Factors Affecting Quantitation

The following list, although not exhaustive, includes many of the major factors affecting spectral response.

Sample Temperature—This parameter is most important for aqueous solutions, where a difference of a few degrees can result in ~~substantial~~ significant spectral changes. Temperature is also an important parameter for solids and powders containing water. Various methods exist to calculate the appropriate temperature correction.

Moisture and Residual Solvents—Moisture present in the sample and analytical system will contribute to bands in the NIR region. Other residual solvents may also contribute to the spectrum.

Sample Thickness—Sample thickness is a known source of spectral variability and must be understood and/or controlled. For example, in reflectance, the sample must be "infinitely" thick, or thinner samples of constant thickness must have a stable, diffusely reflecting backing material of constant, and preferably high, reflectivity.

Sample Optical Properties—In solids, both surface and bulk scattering properties of calibration standards and analytical samples must be taken into account. Spectra of physically, chemically, or optically heterogeneous samples may require sample averaging by increasing the beam size or examining multiple samples. Certain factors, such as differing degree of compaction or particle size in powdered materials and surface finish of samples, can cause significant spectral differences.

Polymorphism—Because NIR reflectance can be measured directly for solid crystalline substances, variations in crystalline structure (polymorphism) influence the spectra. Hence, polymorphs, as well as the amorphous form of a solid, may be distinguished from one another on the basis of their NIR spectra. Where multiple polymorphs can coexist in an otherwise chemically pure bulk drug substance, care

must be taken to ensure that the calibration standards have a distribution of polymorphs relevant to the intended application.

Age of Samples—Samples may exhibit changes in their chemical, physical, or optical properties over time. Care must be taken to ensure that samples for NIR analysis are representative of those used for calibration. If samples of different age are to be analyzed, potential differences in properties must be accounted for in the calibration sample set.■2S (*USP27*)

Delete the following:

■~~**NEAR-INFRARED REFLECTANCE REFERENCES**~~

~~NIR reflectance relies on a background spectrum for the calculation of absorbance. The references (for instance, powders such as barium sulfate or polytetrafluoroethylene and solids such as ceramic or sintered polytef plate) perform essentially the same function in the reflectance measurements as do the solvent blanks in the transmittance measurements. Most NIR measurements are performed in single-beam instruments: the reflectance of a background reference is scanned to obtain a baseline, and then the reflectance of one or more analytical samples is measured. An important property of a reflectance background reference is its uniform reflectance response as a function of wavelength across the spectral range of the instrument. If the background reflectance is not uniform with wavelength, a correction must be calculated. Another important property of the reference is its stability over time. Only spectra measured against the same background reference can be compared with one another. In order to minimize positioning effects, the diameter of the reference sample is at least 125% that of the beam. From measurements in which the background is used as a reference and a sample, a spectrum of the inherent instrument noise as a function of wavelength can be obtained. [NOTE—Instruments based on an integrating sphere geometry can use a sample of the sphere material for the noise measurement.]~~■2S (*USP27*)

Delete the following:

■~~**APPARATUS**~~

~~All NIR measurements are based on passing light radiation through, or into, a sample and measuring the attenuation of the emerging (transmitted or reflected) beam. There is a variety of spectrophotometers and spectrometers based on different operating principles. Dispersive devices include double-beam extended-range UV-visible spectrophotometers, single-beam grating-based rapid-scanning spectrometers, and diode-array spectrometers. Filter technology is employed in fixed- or multiple-wavelength instruments as well as acousto-optical tunable filter (AOTF) spectrometers. Extended range Fourier-transform IR (FTIR) spectrometers are also available. Silicon, lead sulfide, or indium gallium arsenide are the most commonly used detector materials. Conventional cuvette sample holders, fiber-optic probes, transmission dip cells, and spinning or traversing sample holders are some of the more common sampling arrangements.~~

~~Many NIR instruments are designed with easy-to-use or automatic, built-in calibration procedures. Therefore, theoretically, it is only necessary to require that such calibrations be done and to specify how often they are to be performed to maintain quality control. In most cases, the autocalibration setup utilizes special internal parts incorporated into the instrument design for this purpose. Because the optical configuration used in the built-in calibration may differ physically from that used in the specific analytical measurement, this configuration is not necessarily applicable to analytical measurements. Also, the commonly employed internal polystyrene film reference calibrator may be subject to aging and attack by solvents and vapors in the laboratory environment. Methods for internal instrument calibration may vary depending on instrument manufacturer, instrument model, or software version. Therefore, detailed functional validation employing external reference standards is required to demonstrate instrument suitability. The use of external reference standards does not imply the omission of the usual internal quality control procedures; rather, it provides independent documentation of the ability of the instrument to perform the specific analysis.~~■2S (*USP27*)

Add the following:

■**INSTRUMENTATION**

Apparatus

All NIR measurements are based on passing light radiation through or into a sample and measuring the attenuation of the emerging (transmitted, scattered, or reflected) beam. There are a variety of spectrophotometers available based on different operating principles.

Some examples of currently available spectrophotometers are the following: filter and grating-based dispersive, acousto-optical tunable filter (AOTF), ~~and~~ Fourier-transform (FT-NIR), and liquid crystal tunable filters (LCTF) systems. Silicon, lead sulfide, indium gallium arsenide and deuterated triglycine sulphate are commonly used detector materials. Conventional cuvette sample holders, fiber-optic probes, transmission dip cells, and spinning or traversing sample holders are some of the more common sampling arrangements.

The selection of the equipment should be based on the intended application, with particular attention being paid to the suitability of the sampling device for the type of sample to be analyzed.

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Near-Infrared Reflectance References

NIR references, by providing a known stable measurement against which other measurements can be compared, are used to eliminate instrumental variations that would affect the measurements.

Transmittance Mode—The measurement of transmittance is dependent on a background transmittance spectrum for its calculation. A transmittance reference can be air, an empty cell, a solvent blank, or in special cases, a reference sample.

Reflectance Mode—The measurement of reflectance is dependent on a background reflectance spectrum for its calculation. Most measurements are performed in single-beam instruments; the reflectance of a background reference is scanned to obtain a baseline, and then the reflectance of one or more analytical samples is measured. Common reflectance references are ceramic, perfluorinated polymers and gold; other suitable materials may be used. Only spectra measured against a background possessing the same optical properties can be directly compared with one another.

Qualification of NIR Instruments

Elements of Qualification—The qualification of an NIR instrument can be divided into three elements:

- Installation Qualification (IQ)
- Operational Qualification (OQ)
- Performance Qualification (PQ)

Installation Qualification—The IQ requirements help ensure that the hardware and software are installed according to vendor and safety specifications at the desired location.

Operational Qualification—In operational qualification, the instrument's performance is controlled with respect to external certified standards to verify that the system operates within target specifications. The purpose of operational qualification is to ensure that an instrument is suitable for its intended application. Because there are so many different approaches to measuring NIR spectra, operational qualification ~~employs traceable external standards that can be used on any instrument.~~ with traceable external standards that can be used on any instrument is desired. The most important property of a reference material is its stability. For example, the commonly employed internal polystyrene-film reference may be subject to aging and attack by solvents and vapors in the laboratory environment. The use of external traceable reference standards does not imply the omission of the instrument's internal quality control procedures. Similiar to any spectrophotometric device, NIR instruments need to be qualified for both wavelength and photometric scale. Maximum and reduced light-flux noise tests are also included.

Performance Qualification—In performance qualification, a quality of fit to an initial scan or group of scans included in the operational qualification is employed. In such an analysis, it is assumed that reference standard spectra collected on a new or a newly repaired, properly operating instrument represent the best ones available. Comparisons of spectra taken over time on the identical reference standards form the basis for evaluating the long-term stability of an

NIR measurement system. The objective is to ensure that no wavelength calibration shift or change in sensitivity occurs during ongoing analysis.

Previous operational qualification has shown that the equipment is acceptable for use; therefore, a single performance ~~verification~~ qualification standard can be used to re-verify performance on a continuing basis. The user may have a method-specific reference sample to perform this kind of control, providing the sample is stable.

Test Details—The specific tests and how frequently they are performed for each level of qualification is dependent on the instrument and intended application.

Wavelength Uncertainty—Potential problems with internal calibration schemes are avoided by specifying appropriate independent external wavelength standards. For the reflectance mode, NIST SRM 1920a[1] and NIST SRM 2035[2] used in the transflectance mode are available. The nature and type of background reference standard must be specified. In transmittance measurements, NIST SRM 2035 rare earth oxide in glass standard, or Holmium oxide solution NIST SRM 2034[3] are available. ~~These standards can be substituted by other traceable wavelength standards.~~ Alternative standards may be used with appropriate justification.

Take one spectrum (with the same spectral resolution used to obtain the certified value) and measure the position of at least three peaks to cover the entire available range. The acceptance limits for SRM 1920a are reported in *Table 1*.

[1] A mixture of dysprosium, holmium, and erbium, NIST SRM 1920a may be obtained from NIST, Gaithersburg, MD 20899: "A Wavelength Standard for the Near-Infrared Based on the Reflectance of Rare Earth Oxides," *J. Res. Natl. Bur. Stds.* **1986,** *91*(5), 243–253. This reference material exhibits useful calibration peaks in the 700- to 2500-nm range. Because there is no available calibration peak above 2000 nm in SRM 1920a, an instrument cannot be considered wavelength-qualified in the 2000- to 2500-nm range.

[2] A rare earth oxide in glass transmission wavelength standard, SRM 2035, has been certified recently by NIST. "Production and Verification of SRM 2035. Near Infrared Transmission Wavelength Standard", *NIST Special Publication* **1999**, 260-102 (in preparation). This standard may be used in transflectance mode, but it is not currently certified for such use.

[3] Holmium oxide solution, NIST SRM 2034, (wavelength standard from 240 to 650 nm) may be used currently in the 650- to 1100-nm region although bands are not certified in this region. "Holmium Oxide Solution wavelength Standard from 240 to 640 nm-SRM 2034", *NBS Special Publication* **1986**, 260-102; "Spectral Transmittance Characteristics of Holmium Oxide in Perchloric Acid", *J. Res. Natl. Bur. Stds*., **1985**. *90*(2), 115–125.

Table 1. Recommended Near-IR Instrument Specifications[a]

Wavelength Uncertainty	SRM 1920a peaks[b] occur at 1261, 1681, and 1935 nm	
Tolerances	±1 nm at 1200 nm	or ±8 cm^{-1} at 8300 cm^{-1}
	±1 nm at 1600 nm	or ±4 cm^{-1} at 6250 cm^{-1}
	±1.5 nm at 2000 nm	or ±4 cm^{-1} at 5000 cm^{-1}
Photometric Linearity	A_{OBS} vs A_{REF} at 1200, 1600, and 2000 nm;[c]	
	slope = 1.0 ± 0.05; intercept = 0.0 ± 0.05	
Spectrophotometric Noise	measured for 100-nm (300 cm^{-1}) segments between 1200 and 2200 nm (8300 and 4500 cm^{-1})	
Average RMS for measurements at high-light flux	less than 0.3×10^{-3}; no RMS noise greater than 0.8×10^{-3}	
Average RMS for measurements at low-light flux	less than 1×10^{-3}; no RMS noise greater than 2.0×10^{-3}	

[a] A maximum nominal instrument bandwidth of 10 nm at 2500 nm or 16 cm^{-1} at 4000 cm^{-1} is appropriate for most applications.

[b] The nominal 1935-nm peak is sensitive to instrument bandwidth. Use the wavelength value supplied with SRM 1920a at the appropriate instrument bandwidth to determine wavelength uncertainty.

[c] A_{OBS} is the observed absorbance, and A_{REF} is the tabulated absorbance of the reference reflectors at each of the three specified wavelengths.

Photometric Linearity—Verification of photometric linearity is demonstrated with a set of transmission standards of known relative transmittance or reflectance standards of known relative reflectance, usually expressed as percent transmittance or reflectance. For reflectance measurements, traceable carbon-doped polymer standards are available. Spectra obtained from reflectance standards are subject to variability as a result of the difference between the experimental conditions under which they were factory-calibrated and those under which they are subsequently put to use. Hence, the percent reflectance values supplied with a set of calibration standards may not be useful in the attempt to establish an "absolute" calibration for a given instrument. Provided that (1) the standards do not change chemically or physically, (2) the same reference background is used as was used to obtain the certified values, and (3) the instrument measures each standard under identical conditions (including precise sample positioning), the reproducibility of the photometric scale will be established over the range of standards used. Subsequent measurements on the identical set of standards give information on long-term stability. Use at least four reference standards in the range 10% to 90%. [NOTE—A typical set of four reflectance references might be 10%, 20%, 40%, and 80% with 1.0, 0.7, 0.4, and 0.1 as their respective absorbances.] If the system is used for analytes with absorbances higher than 1.0, add a 2% or a 5% standard, or both, to the set. The specifications are reported in *Table 1*.

Spectrophotometric Noise—NIR instrument software may include built-in procedures to automatically determine system noise and to provide a statistical report of noise or signal-to-noise ratio over its operating range. As previously

discussed, it is desirable to supplement such checks with measurements that do not rely directly on manufacturer-supplied procedures. If the qualification procedures in the NIR software do not comply with the contents of this chapter, it is recommended to supplement such checks with measurements that do not rely directly on manufacturer-supplied procedures. The method involves measuring spectra of high- and low-reflectance traceable reference materials. For transmittance modules there are no standards for the low-flux noise test at this time, so it is only possible to perform the high-flux noise test.

HIGH-FLUX NOISE—The instrument noise is evaluated at high-light flux by measuring reflectance or transmittance of the reference standard, with the reference material (e.g., 99%, reflectance standard) acting as both the sample and the background reference. The analysis is performed by tabulating RMS noise levels in successive nominal 100-nm (300 cm^{-1}) spectral segments across the instruments range. The limits are reported in *Table 1*.

LOW-FLUX NOISE—The same procedure may be used with a lower-reflectivity reference material (e.g., 10% reflectance standard) to determine system noise at reduced light flux. The source, optics, detector, and electronics make significant contributions to the noise under these conditions. The limits are reported in *Table 1*.■2S (*USP27*)

Delete the following:

■~~QUALIFICATION AND VERIFICATION OF NEAR INFRARED INSTRUMENTS~~

~~The suitability of a specific instrument for use in a given method is ensured by both the routine, periodic instrument operational qualifications and the more frequent performance verifications (see *Definition of Terms and Symbols*). The purpose of instrument qualification is to ensure that an instrument is suitable for its intended application and, when requalified periodically, continues to function properly over extended time periods. When the device is used for a specific qualitative or quantitative analysis, regular performance verifications are made. Because there are many different approaches to measuring NIR spectra, instrument operational qualification and performance verification employ external standards that can be used on any instrument. As with any spectrophotometric device, an NIR instrument needs to be qualified for both wavelength accuracy and absorbance- or reflectance-scale photometric precision. Maximum and reduced light flux noise tests are also included.~~

~~In performance verification, a quality of fit to an initial scan or group of scans included in the instrument qualification is employed. In such analysis, it is assumed that reference standard spectra collected on a new or a newly repaired, properly operating instrument represent the best available. Comparisons of spectra taken over time on the identical reference standards form the basis for evaluating the long-term stability of an NIR measurement system.~~

~~NOTE—Some instrument software may impose smoothing (see *Definition of Terms and Symbols* and *Spectrophotometric Noise*) to remove noise effects. Smoothing is to be set at a minimum or made to match the required operating conditions for the analysis. The number of scans averaged matches that used in regular operation.~~

~~Frequency of Testing~~

~~Instrument qualification is performed at designated intervals or following a repair or optical reconfiguration, such as lamp replacement or substitution of a tablet analyzer accessory by a fiber optic probe. Tests include wavelength uncertainty, absorbance scale linearity, and high- and low-light flux noise tests. Instrument qualification tests require that specific tolerances be met. If the normal reference standards cannot be used with the operating instrument configuration, then a suitable alternate standard is run in that configuration for use in the performance verification.~~

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Performance verification is carried out on the instrument configured for measurements and is done more frequently than instrument qualification. Performance verification includes wavelength uncertainty, absorbance scale linearity, and high light level noise tests. Wavelength uncertainty and absorbance scale linearity tests may be needed prior to any data collection on a given day. Performance is verified by matching the current spectra to those collected during the previous instrument qualification.

Instrument Operational Qualification

Wavelength uncertainty, photometric linearity, and spectrophotometric noise level specifications recommended for many pharmaceutical analysis applications are shown in *Table 1*. Validation of an analytical method requires establishment of the suitability through testing of each of these specifications. [NOTE—Specifications in *Table 1* are based on the results of a collaborative study. The same principles apply outside of the range covered in this discussion.]

Table 1. Recommended Near-IR Instrument Specifications[a]

Wavelength Uncertainty Tolerances	SRM 1920a peaks[b] occur at 1261, 1681, and 1935 nm	
	±1 nm at 1200 nm	or ±8 cm^{-1} at 8300 cm^{-1}
	±1 nm at 1600 nm	or ±4 cm^{-1} at 6250 cm^{-1}
	±1.5 nm at 2000 nm	or ±4 cm^{-1} at 5000 cm^{-1}
Photometric Linearity	A_{OBS} vs A_{REF} at 1200, 1600, and 2000 nm;[c] slope = 1.0 ± 0.05; intercept = 0.0 ± 0.05	
Spectrophotometric Noise	measured for 100 nm (300 cm^{-1}) segments between 1200 and 2200 nm (8300 and 4500 cm^{-1})	
Average RMS for measurements—at high light flux	less than 0.3×10^{-3}; no RMS noise greater than 0.8×10^{-3}	
Average RMS for measurements—at low light flux	less than 1×10^{-3}; no RMS noise greater than 2.0×10^{-3}	

[a] A maximum nominal instrument bandwidth of 10 nm at 2500 nm or 16 cm^{-1} at 4000 cm^{-1} is appropriate for most applications.
[b] The nominal 1935-nm peak is sensitive to instrument bandwidth. Use the wavelength value supplied with SRM 1920a at the appropriate instrument bandwidth to determine wavelength uncertainty.
[c] A_{OBS} is the observed absorbance, and A_{REF} is the tabulated absorbance of the reference reflectors at each of the three specified wavelengths.

Wavelength Uncertainty—[NOTE—The method used in developing wavelength uncertainty values is based on the NIST Center of Gravity algorithm.] Potential problems with internal calibration schemes are avoided by specifying appropriate independent external wavelength standards. For the reflectance mode, the NIST SRM 1920a reflectance standard is preferred.[1] Standards containing dysprosium or holmium oxide are available. The nature and type of background reference standard must also be specified. In transmittance measurements, the corresponding rare earth solution[2] or glass standards can be used. Solid or sealed standards can be maintained similarly to a set of calibration weights to provide information on long-term stability.[3]

Photometric Linearity—Photometric qualification is based on a set of transmission or reflectance standards of known relative transmittance, or reflectance, usually expressed as percent transmittance or reflectance. Spectra obtained from reflectance standards are subject to variability due to the difference between the experimental conditions under which they are factory calibrated and those under which they are subsequently used. Hence, the percent reflectance values supplied with a set of calibration standards may not be useful to establish an "absolute" calibration for a given instrument. However, as long as the standards have the same physical description, the same reference background is used, and the target instrument measures each under identical settings, the reproducibility of the photometric scale will be established over the range of standards used. Subsequent measurements on the identical set of standards give information on long-term stability. For analytes with absorbances below 1.0, use at least four reference standards in the range 10% to 90%. [NOTE—Lead sulfide or indium gallium arsenide detectors have nearly linear response to absorbances below 2.0, but the instrument design can affect the overall response linearity; hence, a need for multipoint calibrations arises.] For analytes with absorbances that exceed 1.0, add a 2% or a 5% standard, or both, to the regular set.

Spectrophotometric Noise—NIR instrument software may include built in procedures to automatically determine system noise and to provide a statistical report of noise or signal-to-noise ratio over its operating range. Significant changes in the tabulated noise level could signal the need for service. As previously discussed, it is desirable to supplement such checks with measurements that do not rely directly on manufacturer-supplied procedures. The method involves measuring spectra of high- and low-reflectance reference materials. The root-mean-square or peak-to-peak noise values (see *Definition of Terms and Symbols*) in the resulting spectra can then be compared to baseline values established for the instrument on the same reference standard used during the last instrument qualification cycle. Peak-to-peak noise comparison can be carried out by visual inspection of overlaid plots. Preferably, a more thorough analysis is performed by tabulating the root-mean-square (RMS) noise level in successive 100-nm (300-cm^{-1}) spectral segments across the instrument's range (see *Definition of Terms and Symbols*). Calculate the RMS noise in the range from 1200 to 2200 nm by selecting a nominal wavelength every 100 nm and by combining all data points in the range ±50 nm from the nominal wavelength; for example, at 1200 nm use all the points collected from 1150 to 1250 nm (see *Table 1*). Find the mean signal strength over the range, and then calculate the root-mean-square deviations from this mean. Use of deviations from the mean value in a range reduces the effect imparted by differences between the two scans.

The instrument noise is evaluated at high light flux by measuring reflectance of the reference standard, the reference standard acting as the sample and the background reference. This gives the

[1] A mixture of dysprosium, holmium, and erbium, NIST SRM 1920 may be obtained from NIST, Gaithersburg, MD 20899: "A Wavelength Standard for the Near-IR Based on the Reflectance of Rare Earth Oxides," *J Res Natl Bur Stand* **1986,** *91(5)*:243–253. This reference material exhibits useful calibration peaks in both the 700- to 1100-nm and 1100- to 2500-nm ranges. Because there is no available calibration peak above 2000 nm in SRM 1920, an instrument cannot be considered wavelength qualified in the 2000- to 2500-nm range.

[2] Holmium oxide solution, NIST SRM 2034, (wavelength standard from 240 to 650 nm) may be used currently in the 650- to 1100-nm region although bands are not certified in this region.

[3] A rare earth oxide in glass transmission wavelength standard, SRM 2035, has been certified recently by NIST. This standard may be used in transflectance mode, but it is not currently certified for such use.

~~inherent noise as a function of wavelength at high light flux. Because this measurement can be done whenever a new reference background is collected, very frequent noise checks can be made easily.~~

~~In a similar procedure, noise measurements using a lower reflectivity reference material, a 10% or less reflectance standard being recommended, are obtained to determine system output at reduced light flux. This occurs when a highly absorbing or very low reflectance sample is measured. The source, optics, detector, and electronics make significant contributions to the noise under these conditions.~~

~~Performance Verification~~

~~The objective is to ensure that no sudden wavelength calibration shift or change in sensitivity occurs during the analysis. Once an instrument has been set up for a specific analytical measurement, it may no longer be possible or desirable to measure the wavelength and photometric qualification reference standards as described above. Provided instrument operational qualification has shown that the equipment is acceptable for use, a single external performance verification standard can be used to reverify function on a continuing basis. The performance verification standard matches the format of the samples in the current analysis as closely as possible and uses the same background spectrum. For example, for tablet samples use a performance verification tablet of approximately the same size and shape and allow scanning conditions to remain identical.[4] Quantitative measurement of this external performance verification standard spectrum checks both the wavelength calibration and the photometric accuracy. Favorable comparison of a series of performance verification spectra demonstrates proper continued operation of the instrument.~~ ■2S (*USP27*)

Add the following:

▪METHOD VALIDATION

Introduction

The objective of the validation of an NIR method, as in the case with the validation of any analytical procedure, is to demonstrate that it is suitable for its intended purpose. Quantitation by NIR is performed by reference to data obtained from a primary method or a calibration set of samples having known composition.

Although NIR is somewhat different from conventional analytical techniques such that validation is generally achieved through the assessment of specialized chemometric parameters, these parameters can still be related to the fundamental validation characteristics required for any analytical method.

Data pretreatment is often a vital step in the chemometric analysis of NIR spectral data. It can be defined as the mathematical transformation of the NIR spectral data to enhance spectral features and/or remove or reduce unwanted sources of variation prior to the development of the calibration model. Calibration is the process of constructing a mathematical model to relate the response from an analytical instrument to the properties of samples. Many suitable chemometric algorithms for data pretreatment and calibration exist; the selection should be based on suitability for the intended use. Any available data transform or algorithm that can be clearly defined in an exact mathematical expression and gives suitable results can be used.

Validation Parameters

Analytical performance characteristics that should be considered for demonstrating the validation of NIR methods are similar to those required for any analytical procedure. A discussion of the general principles that apply is found in *Validation of Compendial Methods* ⟨1225⟩. These principles should be considered typical for NIR procedures, but exceptions should be dealt with on a case-by-case basis. For qualitative NIR methods, refer to *Analytical Performance Characteristics for Category IV* assays under *Validation of Compendial Methods* ⟨1225⟩; quantitative NIR methods will correspond to the *Analytical Performance Characteristics* for *Category I* and *Category II* assays in the chapter. Specific acceptance criteria for each validation parameter must be consistent with the intended use of the method. The samples used for validation should be independent of the calibration set.

[4] ~~USP has two materials suitable for performance verification. For powder work, Calcium Ascorbate is available as a reference calibrator. For most tablets, Acetaminophen Tablets can be supplied as a reference material.~~

In-Process Revision

Specificity—The extent of specificity testing is dependent on the intended application. Lack of specificity of the NIR method can be compensated by other supporting analytical procedures.

Demonstration of specificity in NIR methods may be accomplished by using the following approaches:

Qualitative

- Potential challenges should be presented to the spectral reference library. These can be materials received on site that are similar to library members in visual appearance, chemical structure, or by name. These challenges must fail identification. Independent samples of materials represented in the library, but not used to create it (i.e., different batches, blends), must give positive identifications when analyzed.

Quantitative

- Wavelengths used in the calibration model can be compared to the known bands of the analyte of interest and those of the matrix to verify that the bands of the analyte of interest are being used in the calibration.
- Wavelengths used for the calibration (e.g., for multiple linear regression models (MLR) or the loadings for the factors used (e.g., for partial least squares [PLS] or principal component regression [PCR] models) can be examined to ~~check if they are using the actual spectroscopic information~~ verify that the actual spectroscopic information results from the analyte of interest.
- For PLS and PCR calibrations, the coefficients can be plotted and the regions of large coefficients compared with the spectrum of the analyte.
- ~~Quantitative measurements may be demonstrated in the presence of variations in the matrix, within the specified method range.~~ Variations in the sample matrix may be shown to have no significant effect on quantitation of the analyte within the specified method range.

Linearity—The validation of NIR linearity involves the demonstration of correlated NIR response to samples distributed throughout the defined range of the calibration model.

Demonstration of linearity in NIR methods may be accomplished using the following approaches:

- The slope and y-intercept (bias) for the predicted validation set can be used together with a plot of the data. Many statistical methods are available for evaluation of the significance of the slope and bias. Other applicable statistics may be used as appropriate.
- Statistical tests such as Durbin–Watson are available for the determination of linearity. Other applicable statistics may be used as appropriate.

The correlation coefficient, ~~r^2~~; r; is not a true measure of linearity, but is rather a measure of the fraction of variation in the data that is adequately modeled by the equation. It is dependent on the standard error of the calibration equation (and hence the reference method) and on the range of the calibration data.

Range—The range of analyte reference values in the validation set defines the range of the NIR method. The range of analyte reference values also effectively defines the quantitation limits for an NIR method. Controls must be in place to ensure that results outside the validated range are not accepted. In certain circumstances, it may not be possible or desirable to extend the validated range to cover the specifications or expected process variability for the entire life cycle of the process. Examples of situations in which only a limited sample range may be available are samples from a controlled manufacturing process and in-process samples. A limited sample set does not preclude the use of an NIR method.

The validation procedure for a quantitative NIR method should generate an outlier result when a sample containing analyte outside of the calibration range is measured. This

outlier result does not necessarily indicate an out-of-specification result. An outlier result from the NIR measurement indicates that further testing of the sample is required. If subsequent testing of the sample by an appropriate method indicates that the analyte content is within specifications, then the sample should be considered to have met those specifications. Thus, measurement of a sample by NIR may generate an outlier result and the sample may still meet specifications for the analyte of interest. For qualitative methods, a batch of material may be outside the space of the original calibration data and fail the identification specification. Acceptable identification of the material must then be established by other appropriate methods.

Accuracy—Accuracy for NIR methods is demonstrated by correlation of NIR results with analytical reference data.

Demonstration of accuracy in NIR methods may be accomplished using the following approaches:

- Accuracy can be indicated by how close the standard error of prediction (SEP) is to the standard error of the reference method used for validation. The error of the reference method may be known on the basis of historical data or a determination of standard error of the laboratory (SEL) may be carried out.
- Several statistical comparison methods can be applied to the predicted validation set and reference values to determine if there is any statistical difference between the results of each method at a specified confidence limit (e.g., paired t-test, bias evaluation).

Precision—Precision of an NIR method expresses the closeness of agreement between a series of measurements under the prescribed conditions. There are two levels of precision that may be considered: repeatability and intermediate precision. The precision of an NIR method is typically expressed as the relative standard deviation of a series of predictions and should be equivalent or better than the precision of the reference method used for validation.

Demonstration of precision in NIR methods may be accomplished using the following approaches:

Repeatability

- Statistical evaluation of a number of replicate measurements of the same sample without variation in sample position.
- Statistical evaluation of multiple sample positionings or aliquots, as appropriate.

Intermediate Precision

- Statistical evaluation of a number of replicate measurements by different analysts on different days.

Robustness—The challenges performed in this category will vary depending on the application and sampling technique. Some of the challenges may be covered as part of the development of the method.

Typical challenges are the following:

- Effect of environmental conditions (e.g., temperature, humidity)
- Effect of sample temperature
- Sample handling (e.g., probe depth, compression of material, sample depth/thickness, sample position)
- Influence of instrument changes (e.g., lamp change, warm up time)

Ongoing Model Evaluation

NIR models validated for use should be the subject of ongoing performance evaluation, which may include the monitoring of accuracy, precision, or other suitable parameters. If unacceptable performance is indicated, corrective action will be necessary. This will involve initial investigations into the cause of the discrepancy and may indicate that the calibration model is not performing satisfactorily. Main-

tenance of the model will then be required and may involve revalidation of the model. The degree of revalidation required depends on the nature of the changes. Appropriate change controls should be established to cover these procedures.

Revalidation of a qualitative model may be necessary as a result of the following:

- Addition of a new material to the spectral reference library
- Changes in the physical properties of the material
- Changes in the source of supply
- Coverage of a wider range of characteristics of a material

Revalidation of a quantitative model may be necessary as a result of the following:

- Changes in the composition of the finished product
- Changes in the manufacturing process
- Changes in the sources or grades of raw materials
- Changes in the reference analytical method
- Major changes to the instrument hardware

Model Transfer

The model for an NIR method is developed, stored and applied in electronic form as part of an appropriate instrument/software package. When a model is transferred to another instrument, procedures and criteria must be applied to demonstrate that the model remains valid on the second instrument. In general, electronic model transfer is only recommended for another instrument of the same type and configuration. A number of model transfer procedures exist and can be applied as appropriate. Procedures involve the use of various chemometric (mathematical and statistical) approaches with appropriate validation.■2S (*USP27*)

Delete the following:

■~~DEFINITION OF TERMS AND SYMBOLS~~

~~ABSORBANCE, *A*, is represented by the equation:~~

~~$$A = -\log(I/I_o) \text{ or } A = -\log T = \log(1/r),$$~~

~~in which, in transmittance measurements, I_o is the intensity of the radiant energy from the source, and includes losses due to solvent absorption, refraction, and scattering when the sample is not present; or in reflectance measurements, I_o is the intensity of radiation indirectly reflected from the background reference material, and also incorporates any losses independent of the sample; I is the intensity of the radiation, at the same wavelength, passing through or reflected from the sample; and T and r are the transmittance and the reflectance, respectively.~~

~~ABSORBANCE SPECTRUM is a display or plot of absorbance as a function of wavelength, in nm, or energy, in cm^{-1}.~~

~~BACKGROUND SPECTRUM is also referred to as a reference spectrum, background reference, or, for reflectance, a white standard. This is a spectrum of transmitted or reflected light intensity as a function of wavelength that does not contain any spectral features due to the analyte. In reflectance measurements, a highly reflective standard reference material is used. A ratio of this spectrum to that of the sample radiation intensities produces a transmittance or reflectance spectrum.~~

~~DATA RESOLUTION is the spacing, in nm or cm^{-1}, between the data points collected in a spectrum.~~

~~DIFFUSE REFLECTANCE is that portion of radiated light penetrating the sample surface, interacting with the analyte material, and being reflected back to the detector. This is the component of the overall reflectance that produces the absorbance spectrum of the sample.~~

~~FIBER OPTIC PROBES generally used in NIR reflectance comprise two components: an optic fiber, which may vary in length and in the number of fibers, and a terminus, which contains specially designed optics for examination of the sample matrix.~~

~~FIBER OPTIC PROBE CONFIGURATION is an instrument setup that incorporates the use of a fiber optic probe. Small lengths of fiber used as components of sampling interfaces are not included in this configuration.~~

~~INSTRUMENT BANDWIDTH—See *Spectral Resolution*.~~

~~INSTRUMENT OPERATIONAL QUALIFICATION, also referred to as instrument qualification, is the process of providing documented evidence that the instrument performs according to its specifications, and that it can perform the intended task. This process is required following any significant change such as instrument installation, relocation, major repair, and so forth.~~

~~INSTRUMENT VERIFICATION—See *Performance Verification*.~~

~~METHOD VALIDATION is the process of establishing and documenting that a developed method of analysis is suitable for its intended application.~~

~~MULTIPLICATIVE SCATTER CORRECTION (MSC) is the spectral preprocessing technique for samples with similar profiles used to minimize spectral differences arising from the discrepancies in characteristics such as particle size, shape, and packing. Other algorithms are also available.~~

~~NOISE SPECTRUM—See *Spectrophotometric Noise*.~~

~~PEAK-TO-PEAK NOISE is the difference between the maximum and the minimum values of absorbance defined within a restricted wavelength or energy range of a noise spectrum.~~

~~PERFORMANCE VERIFICATION, also known as instrument verification, is the process of using one or more well-characterized and stable reference materials to verify that instrument response is equivalent to that previously characterized. Verification may employ the same or different standards for different performance characteristics.~~

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PERFORMANCE VERIFICATION STANDARD is a reference material used to establish consistent instrument performance with respect to wavelength and absorbance scale precision.

PHOTOMETRIC PERFORMANCE VERIFICATION, also referred to as the absorbance scale performance verification, is the process of verifying the response of the photometric scale of an instrument. This requires a minimum of four transmittance or reflectance standards spanning the range from 10% to 90%. [NOTE—A typical set of four reflectance references might be 10%, 20%, 40%, and 80% with 1.0, 0.7, 0.4, and 0.1 as their respective absorbances.] Transmittance standards are not currently available.

POLYMORPHISM is the property of crystallizing in two or more crystalline forms. Such solids, called polymorphs, have the same chemical composition (empirical formula) and molecular structure but differ in the arrangement or conformation of the molecules in the crystal lattice.

REFERENCE SPECTRUM—See *Background Spectrum*.

REFLECTANCE is described by the equation:

$$r = I/I_0;$$

in which I is the intensity of radiation reflected from the surface of the sample; and I_0 is the intensity of radiation reflected from a background reference material and incorporates losses due to solvent absorption, refraction, and scattering.

ROOT MEAN SQUARE (RMS) NOISE is reported for the mid-point of the selected spectral range, and it is calculated by the equation:

$$RMS\ Noise = \sqrt{\frac{1}{N}\sum_{i}^{Segment}(A_i - \bar{A})^2},$$

in which A_i is the absorbance for each data point; and $\bar{A}$ is the mean absorbance over the spectral segment, typically 100-nm segment, of N data points.

SMOOTHING is the process of averaging or otherwise fitting neighboring data points in a spectrum to achieve noise suppression.

SPECTRAL RESOLUTION, also called instrument bandwidth, is a measure of the ability of a spectrometer to separate adjacent narrow spectral lines. Spectral resolution of an instrument is affected by all optical elements in the system, namely, the source geometry, apertures, lenses, mirrors, detector elements, diffraction grating, etc. The line width at half intensity of a narrow-band laser source or a very sharp absorption peak can be used to measure resolution.

SPECTROPHOTOMETRIC NOISE is also referred to as noise spectrum. High flux and low flux determinations exist. In high flux transmittance measurements, the baseline absorbance spectrum is obtained in the absence of the sample. For high flux reflectance measurements, the absorbance spectrum of the 100%r standard reference material is obtained using the same 100%r standard as the reference and the sample. Low flux transmittance spectrum employs a 10%T neutral density reference filter. [NOTE—In single-beam transmittance, the 10%T filter may be used as the reference spectrum.] For low flux reflectance measurement, the absorbance spectrum of a 10%r standard material is obtained by using the same 10%r standard as the reference spectrum.

SPECULAR REFLECTANCE, also known as mirror reflection, is that portion of the radiation not interacting with the sample but simply reflecting back from the sample surface layer (sample-air interface).

TRANSFLECTANCE is a transmittance measurement technique where the radiation traverses the sample twice, the second time after being reflected from a surface behind the sample.

TRANSMITTANCE is represented by the equation:

$$T = I/I_0 \text{ or } T = 10^{-A};$$

in which I is the intensity of the radiation transmitted through the sample; I_0 is the intensity of the radiant energy incident on the sample and includes losses due to solvent absorption, refraction, and scattering; and A is the absorbance.

WAVELENGTH CALIBRATION is the process by which an internal standard material, such as polystyrene, is used to correct the wavelength scale applied to the sensor responses. This process is typically predefined in the software and hardware configuration of the instrument.

WAVELENGTH VERIFICATION is the process of using a wavelength verification standard (e.g., SRM 1920a) to verify the wavelength uncertainty of an instrument. ■2S (*USP27*)

Add the following:

▪GLOSSARY

ABSORBANCE, A, is represented by the equation:

$$A = -\log T = \log (1/T) \text{ or } A = \log (I/R)$$

in which T and R are the transmittance and the reflectance, respectively.

BACKGROUND SPECTRUM is also referred to as a reference spectrum or background reference. A ratio of this spectrum to that of the sample radiation intensities produces a transmittance or reflectance spectrum. For example, in reflectance measurements, a highly reflective standard reference material is used.

CALIBRATION MODEL is a mathematical expression to relate the response from an analytical instrument to the properties of samples.

DIFFUSE REFLECTANCE is that portion of radiated light penetrating the sample surface, interacting with the analyte material, and being reflected back to the detector. This is the component of the overall reflectance that produces the absorbance spectrum of the sample.

DURBIN–WATSON is a method of testing the linearity of a calibration by comparing the sum of squares of successive calibration residuals to the sum of squares of the calibration

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residuals around their mean. The expected value of the Durbin–Watson statistic for random, independent, normally distributed residuals is two.

FIBER-OPTIC PROBES consist of two components: optical fibers, which may vary in length and in the number of fibers, and a terminus, which contains specially designed optics for examination of the sample matrix.

INSTRUMENT BANDWIDTH—is a measure of the ability of a spectrometer to separate radiation of similar wavelengths.

MULTIPLE LINEAR REGRESSION is a calibration algorithm used to relate the response from an analytical instrument to the properties of samples. The distinguishing feature of this algorithm is the use of a limited number of independent variables. Linear-least-squares calculations are performed to establish a relationship between these independent variables and the properties of the samples.

OPERATIONAL QUALIFICATION is the process by which it is demonstrated and documented that the instrument performs according to specifications, and that it can perform the intended task. This process is required following any significant change such as instrument installation, relocation, major repair, etc.

PARTIAL LEAST SQUARES (PLS) is a calibration algorithm used to relate instrument responses to the properties of samples. The distinguishing feature of this algorithm is that, while similar to PCR, this algorithm includes data concerning the properties of the samples used for calibration in the calculation of the factors used to describe the instrument responses.

PERFORMANCE QUALIFICATION, ~~also known as performance verification,~~ is the process of using one or more well-characterized and stable reference materials to verify consistent instrument performance. Qualification may employ the same or different standards for different performance characteristics.

PHOTOMETRIC LINEARITY, also referred to as photometric verification, is the process of verifying the response of the photometric scale of an instrument.

PRINCIPAL COMPONENT REGRESSION (PCR) is a calibration algorithm used to relate the response from an analytical instrument to the properties of samples. This algorithm, which expresses a set of independent variables as a linear combination of factors, is a method of relating those factors to the properties of the samples for which the independent variables were obtained.

REFERENCE SPECTRUM—See *Background Spectrum.*

REFLECTANCE is described by the equation:

$$R = I/I_r,$$

in which I is the intensity of radiation reflected from the surface of the sample; and I_r is the intensity of radiation reflected from a background reference material and its incorporated losses due to solvent absorption, refraction, and scattering.

ROOT-MEAN-SQUARE (RMS) NOISE is calculated by the equation:

$$RMS = \sqrt{\frac{\sum_{i=1}^{N}(A_{1i} - A_{2i})^2}{N}}$$

$$RMS = \sqrt{\frac{1}{N} \times \sum_{i}^{N}\left(A_i - \overline{A}\right)^2},$$

~~in which A_{ik} (with $k = 1,2$) is the value for each data point;~~ in which A_i is the absorbance for each data point; $\overline{A}$ is the mean absorbance over the spectral segment; and N is the number of points per segment.

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SPECTRAL REFERENCE LIBRARY is a collection of spectra of known materials used for the purpose of comparison with unknown materials. The term is commonly used in connection with qualitative methods of spectral analysis (e.g., identification of materials).

STANDARD ERROR OF THE LABORATORY (SEL) is a calculation based on repeated readings of one or more samples to estimate the precision and/or accuracy of the reference laboratory method, depending on how the data was collected.

STANDARD ERROR OF PREDICTION (SEP) is a measure of accuracy of an analytical method based on applying a given calibration model to the spectral data from a set of samples different from but similar to those used to calculate the calibration model. The SEP is the standard deviation of the residuals obtained from comparing the values from the reference laboratory to those from the method under test, for the specified samples. The SEP provides a measure of the accuracy expected when measuring future samples.

SURFACE REFLECTANCE, also known as specular reflection, is that portion of the radiation not interacting with the sample but simply reflecting back from the sample surface layer (sample-air interface).

TRANSFLECTANCE is a transmittance measurement technique in which the radiation traverses the sample twice, the second time after being reflected from a surface behind the sample.

TRANSMITTANCE is represented by the equation:

$$T = I/I_0 \text{ or } T = 10^{-A},$$

in which I is the intensity of the radiation transmitted through the sample; I_0 is the intensity of the radiant energy incident on the sample and includes losses due to solvent absorption, refraction, and scattering; and A is the absorbance.■2S (*USP27*)

REAGENTS, INDICATORS, AND SOLUTIONS

Reagent Specifications

BRIEFING

Cesium Chloride. This new reagent is specified in the test for *Sodium content* under *Enoxaparin Sodium* appearing elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—40322-1

Add the following:

■**Cesium Chloride**—**168.4** [*7647-17-8*]—White fine crystals. Use a suitable grade.■2S (*USP27*)

BRIEFING

Deuterated Methanol. This new reagent is used in *Identification B* under *Enoxaparin Sodium,* appearing elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—40321-1

Add the following:

■**Deuterated Methanol** *(Methanol-^{12}C-d_4, Methyl-^{12}C-d_3 alcohol-d_1)*—**36.1** [*811-98-3*] The degree of deuteration is not less than 99.8%. Is a clear colorless liquid miscible with water, with alcohol, and with methylene chloride; density at 20°: 0.888 g/mL, refractive index at 20° (D-line): 1.326; boiling point 65.4° (760 mm Hg).■2S (*USP27*)

In-Process Revision

BRIEFING

Melamine. This new reagent is used to prepare the *Resolution solution* in the test for *Related compounds* under *Metformin Hydrochloride* and *Metformin Hydrochloride Tablets,* which appear elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—34256-1

Add the following:

■**Melamine** *(2,4,6-Triamino-1,3,5-triazine)*, $C_3H_6N_6$—**126.1** [*108-78-1*]—Use a suitable grade.■2S (*USP27*)

BRIEFING

Pyridoxal 5-Phosphate, *USP 26* page 2505. It is proposed to revise the quality requirements of this reagent to reflect the material that is currently available on the market.

(HDQ: M. Marques) RTS—40271-1

Change to read:

Pyridoxal 5-Phosphate, 4-$CHOC_5HN$-2-CH_3, 3-OH, 5-$CH_2PO_4H_2 \cdot H_2O$—**265.16**—Light yellow powder.

~~*Assay*—Transfer about 500 mg, accurately weighed, to a suitable flask. Add 20.0 mL of 0.5 *N* sodium hydroxide VS and 130 mL of water and heat under reflux for 1 hour. Cool, transfer the solution to a 250-mL beaker, rinse the flask with about 30 mL of water and add the rinsing to the beaker. Titrate the solution with 0.5 *N* hydrochloric acid VS, determining the first endpoint potentiometrically. Perform a blank determination and make any necessary correction. Each mL of 0.1 *N* sodium hydroxide consumed is equivalent to 8.839 mg of $C_8H_{10}NO_6P \cdot H_2O$. not less than 95% is found.~~

~~*Melting range* ⟨741⟩: between 140° and 143°, with decomposition.~~

~~*Water, Method I* ⟨921⟩: between 8.5% and 9.5%.~~

■Use a suitable grade.■2S (*USP27*)

BRIEFING

Thrombin Human *(Factor II_a)*. This new reagent is used in the test for *Anti-factor II_a activity content* under *Enoxaparin Sodium* and *Enoxaparin Sodium Injection* appearing elsewhere in this number of *PF.*

(HDQ: M. Marques) RTS—40323-1

Add the following:

■**Thrombin Human** *(Factor II_a)*—**~33,600 [***9002-04-4***]**—A preparation of a serine protease (enzyme) that converts human fibrinogen into fibrin. It is obtained from human plasma and may be prepared by precipitation with suitable salts and organic solvents under controlled conditions of pH, ionic strength, and temperature. A yellowish-white powder, freely soluble in a 9 g per L solution of sodium chloride, which forms a cloudy, pale yellow solution. Store in a sealed, sterile container under nitrogen, protected from light, at a temperature below 0°. One unit corresponds to the amount of enzyme that hydrolyzes 1 µmol of Tos-Gly-Pro-Arg-4-nitroaniline acetate per minute at a pH of 8.4 and at a temperature of 37°.■2S (*USP27*)

REFERENCE TABLES

BRIEFING

Container Specifications for Capsules and Tablets, *USP 26* page 2540, and page 1683 of *PF* 29(5) [Sept.–Oct. 2003].

(HDQ) RTS—34256-1; 39659-1; 39774-1; 39803-1

The following table is provided as a reminder for the pharmacist engaged in the typical dispensing situation who already is acquainted with the *Packaging and storage* requirements set forth in the individual monographs. It lists the capsules and tablets that are, or will be, official in the *United States Pharmacopeia* and indicates the relevant tight (T), well-closed (W), and light-resistant (LR) specifications applicable to containers in which the drug that is repackaged should be dispensed.

This table is not intended to replace, nor should it be interpreted as replacing, the definitive requirements stated in the individual monographs.

Container Specifications for Capsules and Tablets

Monograph Title	*Container Specification*
Change to read:	
Acepromazine Maleate Tablets	~~W~~ ■T, ■1S (*USP27*) LR
Change to read:	
Acetaminophen, Aspirin, and Caffeine Tablets	~~W~~ ■T■1S (*USP27*)
Change to read:	
Acetazolamide Tablets	~~W~~ ■T■1S (*USP27*)
Change to read:	
Acetohexamide Tablets	~~W~~ ■T■1S (*USP27*)
Change to read:	
Albuterol Tablets	~~W~~ ■T,■1S (*USP27*) LR
Add the following:	
■Alendronate Sodium Tablets	T■1S (*USP27*)
Change to read:	
Allopurinol Tablets	~~W~~ ■T■1S (*USP27*)
Change to read:	
Alumina and Magnesia Tablets	~~W~~ ■T■1S (*USP27*)
Change to read:	
Alumina, Magnesia, and Calcium Carbonate Tablets	~~W~~ ■T■1S (*USP27*)
Change to read:	
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets	~~W~~ ■T■1S (*USP27*)
Add the following:	
■Benazepril Tablets	W■1S (*USP27*)
Add the following:	
■Bisoprolol Fumarate and Hydrochlorothiazide Tablets	W■1S (*USP27*)
Add the following:	
■Cefaclor Tablets	T■2S (*USP27*)
Add the following:	
■Clarithromycin Tablets, Extended-Release	W■2S (*USP27*)
Add the following:	
■Black Cohosh Tablets	T, LR■1S (*USP27*)
Add the following:	
■Desogestrel and Ethinyl Estradiol Tablets	W■1S (*USP27*)
Add the following:	
■Fluoxetine Capsules, Delayed-Release	T■1S (*USP27*)
Add the following:	
■Gabapentin Capsules	W■1S (*USP27*)
Add the following:	
■Ginkgo Capsules	T, LR■1S (*USP27*)
Add the following:	
■Ginkgo Tablets	T, LR■1S (*USP27*)
Add the following:	
■Irbesartan Tablets	W■1S (*USP27*)
Add the following:	
■Irbesartan and Hydrochlorothiazide Tablets	W■1S (*USP27*)
Add the following:	
■Isosorbide Mononitrate Tablets	T■1S (*USP27*)
Add the following:	
■Isosorbide Mononitrate Tablets, Extended-Release	T■1S (*USP27*)
Add the following:	
■Isradipine Capsules	T■1S (*USP27*)
Add the following:	
■Kava Capsules	T, LR■1S (*USP27*)

In-Process Revision

Monograph Title	*Container Specification*
Add the following:	
■Kava Tablets	T, LR■1S (*USP27*)
Add the following:	
■Loratadine Tablets	T■1S (*USP27*)
Add the following:	
■Metformin Hydrochloride Tablets	T■2S (*USP27*)
Add the following:	
■Metolazone Tablets	T, LR■2S (*USP27*)
Change to read:	
Nabumetone Tablets	~~T~~ ▲W▲*USP27*
Add the following:	
■Naratriptan Tablets	T■1S (*USP27*)
Add the following:	
■Norgestimate and Ethinyl Estradiol Tablets	W■1S (*USP27*)
Add the following:	
■Oxaprozin Tablets	T, LR■1S (*USP27*)
Add the following:	
■Paroxetine Hydrochloride Tablets	W■1S (*USP27*)
Add the following:	
■Quinapril Tablets	W■1S (*USP27*)
Add the following:	
■Valsartan Capsules	T, LR■1S (*USP27*)
Add the following:	
■Valsartan and Hydrochlorothiazide Tablets	W■1S (*USP27*)

BRIEFING

Description and Relative Solubility of USP and NF Articles, *USP 26* page 2546, page 3179 of the *Second Supplement*, page 5310 of *PF* 23(6) [Nov.–Dec. 1997], page 7017 of *PF* 24(5) [Sept.–Oct. 1998], page 8282 of *PF* 25(3) [May–June 1999], page 8589 of *PF* 25(4) [July–Aug. 1999], page 8917 of *PF* 25(5) [Sept.–Oct. 1999], page 9254 of *PF* 25(6) [Nov.–Dec. 1999], page 504 of *PF* 26(2) [Mar.–Apr. 2000], page 837 of *PF* 26(3) [May–June 2000], page 1135 of *PF* 26(4) [July–Aug. 2000], page 1385 of *PF* 26(5) [Sept.–Oct. 2000], page 1907 of *PF* 27(1) [Jan.–Feb. 2001], page 2281 of *PF* 27(2) [Mar.–Apr. 2001], page 2839 of *PF* 27(4) [July–Aug. 2001], page 3374 of *PF* 27(6) [Nov.–Dec. 2001], page 554 of *PF* 28(2) [Mar.–Apr. 2002], page 853 of *PF* 28(3) [May–June 2002], page 1236 of *PF* 28(4) [July–Aug. 2002], page 1542 of *PF* 28(5) [Sept.–Oct. 2002], page 1953 of *PF* 28(6) [Nov.–Dec. 2002], page 266 of *PF* 29(1) [Jan.–Feb. 2003], page 509 of *PF* 29(2) [Mar.–Apr. 2003], page 812 of *PF* 29(3) [May–June 2003], page 1262 of *PF* 29(4) [July–Aug. 2003], and page 1684 of *PF* 29(5) [Sept.–Oct. 2003].

(HDQ) RTS—34256-1; 37702-1; 39641-2; 40086-1

Add the following:

■**Ammonio Methacrylate Copolymer Dispersion:** Milky-white liquids of low viscosity with a faint characteristic odor. Miscible with water in any proportion, the milky-white appearance being retained. A clear or slightly cloudy solution is obtained on mixing one part with five parts of acetone, alcohol, or isopropyl alcohol. When mixed with methanol in a ratio of 1:5, Ammonio Methacrylate Copolymer Dispersion Type A dissolves completely, and Ammonio Methacrylate Copolymer Dispersion Type B dissolves only partially. *NF category:* Coating agent.■2S (*USP27*)

Add the following:

■**Carbomer Homopolymer:** White, fluffy hydroscopic powder, having a slight, characteristic odor. The pH of a 1 in 100 dispersion in water is about 3. When neutralized with alkali hydroxides or with amines, it swells giving the appearance of dissolving in water; when neutralized with lower amines and alkanolamines, it swells giving the appearance of dissolving in methanol or glycerin; when neutralized with ethoxylated long-chain (C_{14}–C_{18}) amines, it

swells giving the appearance of dissolving in ethanol. *NF category:* Tablet binder; suspending and/or viscosity-increasing agent.■2S (*USP27*)

Add the following:

■**Glimepiride:** White to almost white powder. Soluble in dimethylformamide; slightly soluble in methanol; sparingly soluble in methylene chloride; practically insoluble in water. It also dissolves in dilute alkali hydroxides and dilute acids.■2S (*USP27*)

Add the following:

■**Metformin Hydrochloride:** White, crystalline powder. Freely soluble in water; slightly soluble in alcohol; practically insoluble in acetone and in methylene chloride.■2S (*USP27*)

Items from Earlier Numbers of PF that Have Not Yet Appeared in a Supplement, and are Therefore Candidates for Subsequent Supplements.

GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"—See PF Vol. 29 No. 4, page 983.
Significant Figures and Tolerances—See PF Vol. 29 No. 4, page 984.
Tests and Assays—See PF Vol. 29 No. 4, page 985.
Preservation, Packaging, Storage, and Labeling—See PF Vol. 29 No. 4, page 988.

USP MONOGRAPHS

Acebutolol Hydrochloride Capsules—See PF Vol. 27 No. 1, page 1743.
Acepromazine Maleate Injection—See PF Vol. 27 No. 3, page 2494.
Acepromazine Maleate Tablets—See PF Vol. 27 No. 3, page 2494.
Acetaminophen—See PF Vol. 27 No. 3, page 2494.
Acetaminophen Capsules—See PF Vol. 27 No. 3, page 2494.
Acetaminophen for Effervescent Oral Solution—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Oral Solution—See PF Vol. 27 No. 3, page 2494.
Acetaminophen Oral Suspension—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Suppositories—See PF Vol. 27 No. 3, page 2495.
Acetaminophen Tablets—See PF Vol. 27 No. 3, page 2495.
Acetaminophen and Aspirin Tablets—See PF Vol. 27 No. 3, page 2495.
Acetaminophen, Aspirin, and Caffeine Tablets—See PF Vol. 27 No. 3, page 2495.
Capsules Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 3, page 2496.
Oral Powder Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 3, page 2496.
Oral Solution Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 6, page 3241.
Tablets Containing at Least Three of the Following—Acetaminophen and Salts of Chlorpheniramine, Dextromethorphan, and Pseudoephedrine—See PF Vol. 27 No. 3, page 2496.
Acetaminophen and Codeine Phosphate Capsules—See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Oral Solution—See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Oral Suspension—See PF Vol. 29 No. 3, page 601.
Acetaminophen and Codeine Phosphate Tablets—See PF Vol. 29 No. 3, page 602.
Acetaminophen, Dextromethorphan Hydrobromide, Doxylamine Succinate, and Pseudoephedrine Hydrochloride Oral Solution—See PF Vol. 27 No. 3, page 2499.
Acetaminophen and Diphenhydramine Citrate Tablets—See PF Vol. 27 No. 3, page 2499.
Acetaminophen, Diphenhydramine Hydrochloride, and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 27 No. 3, page 2499.
Acetaminophen and Pseudoephedrine Hydrochloride Tablets—See PF Vol. 27 No. 3, page 2500.
Acetazolamide—See PF Vol. 27 No. 3, page 2500.
Acetazolamide for Injection—See PF Vol. 27 No. 3, page 2500.
Acetazolamide Tablets—See PF Vol. 27 No. 3, page 2501.
Glacial Acetic Acid—See PF Vol. 27 No. 3, page 2501.
Acetic Acid Irrigation—See PF Vol. 27 No. 3, page 2501.
Acetic Acid Otic Solution—See PF Vol. 27 No. 3, page 2501.
Acetohexamide—See PF Vol. 27 No. 3, page 2501.
Acetohexamide Tablets—See PF Vol. 27 No. 3, page 2501.
Acetohydroxamic Acid Tablets—See PF Vol. 27 No. 3, page 2503.
Acetylcholine Chloride—See PF Vol. 27 No. 3, page 2502.
Acetylcholine Chloride for Ophthalmic Solution—See PF Vol. 27 No. 3, page 2502.
Acetylcysteine—See PF Vol. 27 No. 3, page 2503.
Acetylcysteine Solution—See PF Vol. 27 No. 3, page 2503.
Acetylcysteine and Isoproterenol Hydrochloride Inhalation Solution—See PF Vol. 27 No. 3, page 2503.
Acyclovir Capsules—See PF Vol. 29 No. 3, page 602.
Acyclovir for Injection—See PF Vol. 29 No. 3, page 602.
Acyclovir Ointment—See PF Vol. 29 No. 3, page 604.
Acyclovir Oral Suspension—See PF Vol. 29 No. 3, page 604.
Acyclovir Tablets—See PF Vol. 29 No. 3, page 604.
Adenine—See PF Vol. 27 No. 3, page 2504.
Albendazole—See PF Vol. 27 No. 3, page 2505.
Albendazole Oral Suspension—See PF Vol. 29 No. 4, page 991.
Albendazole Tablets—See PF Vol. 27 No. 3, page 2505.
Albumin Human—See PF Vol. 29 No. 4, page 992.
Albuterol—See PF Vol. 27 No. 3, page 2505.
Albuterol Sulfate—See PF Vol. 27 No. 3, page 2506.
Albuterol Tablets—See PF Vol. 27 No. 3, page 2506.
Alclometasone Dipropionate—See PF Vol. 27 No. 3, page 2506.
Alclometasone Dipropionate Cream—See PF Vol. 27 No. 3, page 2507.
Alclometasone Dipropionate Ointment—See PF Vol. 27 No. 3, page 2507.
Alcohol—See PF Vol. 27 No. 3, page 2507.
Dehydrated Alcohol—See PF Vol. 27 No. 3, page 2507.
Dehydrated Alcohol Injection—See PF Vol. 27 No. 3, page 2507.
Rubbing Alcohol—See PF Vol. 27 No. 3, page 2507.
Alcohol in Dextrose Injection—See PF Vol. 27 No. 3, page 2508.
Alendronate Sodium—See PF Vol. 28 No. 3, page 737.
Alendronate Sodium Tablets—See PF Vol. 28 No. 3, page 740.
Alendronic Acid Tablets—See PF Vol. 29 No. 4, page 997.
Allopurinol—See PF Vol. 28 No. 5, page 1387.
Allopurinol Oral Solution—See PF Vol. 29 No. 4, page 1000.
Allopurinol Tablets—See PF Vol. 29 No. 3, page 604.
Allyl Isothiocyanate—See PF Vol. 27 No. 3, page 2509.
Alprostadil—See PF Vol. 29 No. 5, page 1412.
Altretamine—See PF Vol. 27 No. 3, page 2514.
Altretamine Capsules—See PF Vol. 27 No. 3, page 2514.
Potassium Alum—See PF Vol. 27 No. 3, page 2515.
Alumina and Magnesia Oral Suspension—See PF Vol. 27 No. 3, page 2515.
Alumina and Magnesia Tablets—See PF Vol. 27 No. 3, page 2515.
Alumina, Magnesia, and Calcium Carbonate Oral Suspension—See PF Vol. 27 No. 6, page 3241.
Alumina, Magnesia, and Calcium Carbonate Tablets—See PF Vol. 27 No. 3, page 2515.
Alumina, Magnesia, Calcium Carbonate, and Simethicone Tablets—See PF Vol. 27 No. 6, page 3241.
Amifostine—See PF Vol. 29 No. 5, page 1413.
Amiloride Hydrochloride and Hydrochlorothiazide Tablets—See PF Vol. 29 No. 3, page 605.
Aminocaproic Acid—See PF Vol. 29 No. 5, page 1414.
Aminopentamide Sulfate—See PF Vol. 29 No. 5, page 1414.
Aminophylline—See PF Vol. 29 No. 5, page 1414.
Ammonium Chloride—See PF Vol. 29 No. 5, page 1415.
Ammonium Molybdate—See PF Vol. 29 No. 5, page 1416.
Amoxicillin Tablets—See PF Vol. 29 No. 1, page 48.
Amoxicillin and Clavulanate Potassium for Oral Suspension—See PF Vol. 29 No. 3, page 605.
Amoxicillin and Clavulanate Potassium Tablets—See PF Vol. 29 No. 3, page 605.
Ampicillin—See PF Vol. 28 No. 6, page 1766.
Amprolium Oral Solution—See PF Vol. 29 No. 3, page 606.

Anthrax Vaccine Adsorbed—See PF Vol. 29 No. 4, page 1002.
L-Asparagine—See PF Vol. 29 No. 3, page 687.
Aspirin and Codeine Phosphate Tablets—See PF Vol. 29 No. 3, page 606.
Atenolol—See PF Vol. 29 No. 5, page 1416.
Atenolol Oral Solution—See PF Vol. 29 No. 4, page 1001.
Atenolol Tablets—See PF Vol. 29 No. 1, page 49.
Atenolol and Chlorthalidone Tablets—See PF Vol. 29 No. 3, page 606.
Atracurium Besylate Injection—See PF Vol. 29 No. 4, page 1008.
Azithromycin—See PF Vol. 29 No. 5, page 1417.
Azithromycin Capsules—See PF Vol. 27 No. 6, page 3394.
Barium Sulfate Paste—See PF Vol. 25 No. 4, page 8479.
BCG Live—See PF Vol. 29 No. 5, page 1419.
Benazepril Hydrochloride—See PF Vol. 29 No. 5, page 1422.
Benazepril Hydrochloride Tablets—See PF Vol. 29 No. 3, page 606.
Benzethonium Chloride Concentrate—See PF Vol. 29 No. 3, page 608.
Betahistine Hydrochloride—See PF Vol. 29 No. 4, page 1008.
Betamethasone—See PF Vol. 29 No. 5, page 1427.
Betamethasone Oral Solution—See PF Vol. 29 No. 4, page 1009.
Betamethasone Syrup—See PF Vol. 29 No. 4, page 1010.
Betamethasone Tablets—See PF Vol. 29 No. 4, page 1011.
Betamethasone Acetate—See PF Vol. 29 No. 5, page 1427.
Betamethasone Benzoate—See PF Vol. 29 No. 5, page 1427.
Betamethasone Benzoate Gel—See PF Vol. 29 No. 5, page 1428.
Betamethasone Dipropionate—See PF Vol. 29 No. 5, page 1428.
Betamethasone Dipropionate Cream—See PF Vol. 29 No. 5, page 1429.
Betamethasone Dipropionate Lotion—See PF Vol. 29 No. 5, page 1430.
Betamethasone Dipropionate Ointment—See PF Vol. 29 No. 5, page 1430.
Betamethasone Dipropionate Topical Aerosol—See PF Vol. 29 No. 5, page 1428.
Bethanechol Chloride—See PF Vol. 29 No. 1, page 52.
Bethanechol Chloride Tablets—See PF Vol. 29 No. 1, page 54.
Bismuth Subsalicylate Oral Suspension—See PF Vol. 28 No. 2, page 627.
Bismuth Subsalicylate Tablets—See PF Vol. 28 No. 5, page 1603.
Bisoprolol Fumarate—See PF Vol. 29 No. 3, page 609.
Bisoprolol Fumarate Tablets—See PF Vol. 29 No. 3, page 610.
Bisoprolol Fumarate and Hydrochlorothiazide Tablets—See PF Vol. 29 No. 3, page 612.
Bleomycin for Injection—See PF Vol. 29 No. 4, page 1011.
Whole Blood—See PF Vol. 29 No. 2, page 445.
Red Blood Cells—See PF Vol. 29 No. 2, page 431.
Bretylium Tosylate—See PF Vol. 29 No. 5, page 1431.
Bromodiphenhydramine Hydrochloride and Codeine Phosphate Syrup—See PF Vol. 27 No. 5, page 2980.
Brompheniramine Maleate—See PF Vol. 29 No. 5, page 1431.
Bumetanide—See PF Vol. 29 No. 5, page 1432.
Bupivacaine Hydrochloride—See PF Vol. 29 No. 5, page 1432.
Bupropion Hydrochloride—See PF Vol. 29 No. 4, page 1011.
Bupropion Hydrochloride Extended-Release Tablets—See PF Vol. 29 No. 4, page 1012.
Butalbital, Acetaminophen, and Caffeine Tablets—See PF Vol. 29 No. 3, page 615.
Calcitriol—See PF Vol. 29 No. 5, page 1433.
Calcitriol Injection—See PF Vol. 29 No. 5, page 1434.
Calcium Chloride—See PF Vol. 29 No. 5, page 1436.
Dibasic Calcium Phosphate—See PF Vol. 22 No. 6, page 3029.
Anhydrous Dibasic Calcium Phosphate—See PF Vol. 22 No. 6, page 2011.
Carbidopa and Levodopa Tablets—See PF Vol. 29 No. 3, page 615.
Carboprost Tromethamine—See PF Vol. 29 No. 5, page 1436.
Cefaclor Capsules—See PF Vol. 29 No. 1, page 56.
Cefadroxil—See PF Vol. 29 No. 5, page 1436.
Cefazolin Ophthalmic Solution—See PF Vol. 28 No. 2, page 261.
Cefepime Hydrochloride—See PF Vol. 29 No. 5, page 1437.
Cefixime—See PF Vol. 29 No. 3, page 616.
Ceftazidime for Injection—See PF Vol. 29 No. 3, page 617.
Cefuroxime Axetil for Oral Suspension—See PF Vol. 29 No. 5, page 1438.
Cefuroxime Axetil Tablets—See PF Vol. 29 No. 4, page 1014.
Chloroprocaine Hydrochloride—See PF Vol. 29 No. 5, page 1438.
Chlorothiazide—See PF Vol. 29 No. 5, page 1439.
Chlorpheniramine Maleate—See PF Vol. 29 No. 5, page 1439.
Chromic Chloride—See PF Vol. 29 No. 5, page 1440.
Ciclopirox—See PF Vol. 29 No. 2, page 393.
Ciclopirox Olamine—See PF Vol. 29 No. 4, page 1015.
Cimetidine—See PF Vol. 29 No. 5, page 1440.
Cimetidine Tablets—See PF Vol. 28 No. 1, page 52.
Ciprofloxacin—See PF Vol. 29 No. 4, page 1017.
Ciprofloxacin Tablets—See PF Vol. 29 No. 4, page 1018.
Clavulanate Potassium—See PF Vol. 29 No. 3, page 617.
Clindamycin Phosphate—See PF Vol. 29 No. 1, page 57.
Clindamycin Phosphate Vaginal Inserts—See PF Vol. 29 No. 3, page 620.
Clonazepam Tablets—See PF Vol. 29 No. 3, page 621.
Clonidine—See PF Vol. 29 No. 1, page 58.
Clonidine Hydrochloride—See PF Vol. 29 No. 5, page 1440.
Clonidine Hydrochloride Injection—See PF Vol. 26 No. 2, page 351.
Clonidine Transdermal System—See PF Vol. 29 No. 5, page 1441.
Clopidogrel Bisulfate—See PF Vol. 29 No. 5, page 1445.
Clotrimazole Vaginal Inserts—See PF Vol. 29 No. 3, page 622.
Clotrimazole Vaginal Tablets—See PF Vol. 29 No. 3, page 623.
Clotrimazole and Betamethasone Dipropionate Cream—See PF Vol. 29 No. 3, page 623.
Clozapine—See PF Vol. 29 No. 3, page 623.
Cortisone Acetate—See PF Vol. 29 No. 5, page 1447.
Cupric Sulfate—See PF Vol. 29 No. 5, page 1447.
Cyanocobalamin Co 57 Capsules—See PF Vol. 29 No. 2, page 397.
Cyanocobalamin Co 57 Oral Solution—See PF Vol. 29 No. 2, page 398.
Cyclandelate—See PF Vol. 29 No. 4, page 1023.
Cyclobenzaprine Hydrochloride—See PF Vol. 29 No. 4, page 1024.
Cyclosporine Capsules—See PF Vol. 27 No. 4, page 2721.
Deferoxamine Mesylate—See PF Vol. 29 No. 5, page 1448.
Demeclocycline Hydrochloride Capsules—See PF Vol. 29 No. 3, page 625.
Demeclocycline Hydrochloride Tablets—See PF Vol. 29 No. 3, page 625.
Deslanoside—See PF Vol. 29 No. 5, page 1448.
Desmopressin Acetate—See PF Vol. 24 No. 2, page 5773.
Desmopressin Injection—See PF Vol. 24 No. 2, page 5778.
Desmopressin Nasal Spray Solution—See PF Vol. 24 No. 2, page 5779.
Desogestrel—See PF Vol. 28 No. 6, page 1785.
Desogestrel and Ethinyl Estradiol Tablets—See PF Vol. 29 No. 5, page 1448.
Desoxycorticosterone Acetate—See PF Vol. 29 No. 5, page 1456.
Dexamethasone Acetate—See PF Vol. 29 No. 5, page 1457.
Dextran 40—See PF Vol. 29 No. 2, page 399.
Dextran 70—See PF Vol. 29 No. 2, page 401.
Dextrose—See PF Vol. 29 No. 5, page 1457.
Diazoxide—See PF Vol. 29 No. 5, page 1458.
Dibucaine Hydrochloride—See PF Vol. 29 No. 5, page 1458.
Dichlorphenamide—See PF Vol. 29 No. 4, page 1025.
Dicyclomine Hydrochloride—See PF Vol. 29 No. 5, page 1458.
Dicyclomine Hydrochloride Capsules—See PF Vol. 29 No. 5, page 1459.
Dicyclomine Hydrochloride Injection—See PF Vol. 29 No. 5, page 1460.
Dicyclomine Hydrochloride Oral Solution—See PF Vol. 29 No. 5, page 1461.

Dicyclomine Hydrochloride Syrup—See PF Vol. 29 No. 5, page 1462.
Dicyclomine Hydrochloride Tablets—See PF Vol. 29 No. 5, page 1462.
Diethylstilbestrol—See PF Vol. 29 No. 5, page 1463.
Diethylstilbestrol Diphosphate Tablets—See PF Vol. 23 No. 1, page 3385.
Dihydroergotamine Mesylate—See PF Vol. 29 No. 5, page 1463.
Dihydroergotamine Mesylate Nasal Solution—See PF Vol. 25 No. 6, page 9078.
Dimenhydrinate—See PF Vol. 29 No. 5, page 1466.
Dimercaprol—See PF Vol. 29 No. 5, page 1466.
Diphenhydramine Hydrochloride—See PF Vol. 29 No. 5, page 1466.
Dipyridamole—See PF Vol. 29 No. 5, page 1467.
Divalproex Sodium Delayed-Release Tablets—See PF Vol. 29 No. 3, page 625.
Dobutamine Hydrochloride—See PF Vol. 29 No. 5, page 1467.
Dolasetron Mesylate—See PF Vol. 29 No. 5, page 1468.
Dolasetron Mesylate Injection—See PF Vol. 29 No. 1, page 60.
Dopamine Hydrochloride—See PF Vol. 29 No. 5, page 1469.
Doxazosin Mesylate—See PF Vol. 29 No. 5, page 1470.
Doxazosin Tablets—See PF Vol. 29 No. 1, page 64.
Doxorubicin Hydrochloride—See PF Vol. 29 No. 1, page 66.
Droperidol—See PF Vol. 29 No. 5, page 1473.
Dyphylline—See PF Vol. 29 No. 5, page 1473.
Edetate Calcium Disodium—See PF Vol. 29 No. 5, page 1474.
Edetate Disodium—See PF Vol. 29 No. 5, page 1474.
Edrophonium Chloride—See PF Vol. 29 No. 5, page 1475.
Egg Phospholipids—See PF Vol. 29 No. 2, page 401.
Enalapril Maleate—See PF Vol. 29 No. 5, page 1475.
Ephedrine Sulfate—See PF Vol. 29 No. 5, page 1476.
Epinephrine—See PF Vol. 29 No. 5, page 1476.
Ergoloid Mesylates Tablets—See PF Vol. 29 No. 5, page 1477.
Ergonovine Maleate—See PF Vol. 29 No. 5, page 1478.
Erythromycin Ethylsuccinate and Sulfisoxazole Acetyl for Oral Suspension—See PF Vol. 29 No. 3, page 626.
Estradiol—See PF Vol. 29 No. 5, page 1478.
Estradiol Transdermal System—See PF Vol. 25 No. 6, page 9080.
Conjugated Estrogens—See PF Vol. 29 No. 5, page 1478.
Estrone—See PF Vol. 29 No. 5, page 1479.
Ethacrynic Acid—See PF Vol. 29 No. 5, page 1479.
Ethotoin—See PF Vol. 29 No. 1, page 66.
Famotidine Tablets—See PF Vol. 29 No. 3, page 627.
Fenoldapam Mesylate—See PF Vol. 29 No. 5, page 1479.
Ferrous Fumarate—See PF Vol. 29 No. 3, page 629.
Ferrous Fumarate and Docusate Sodium Extended-Release Tablets—See PF Vol. 29 No. 4, page 1026.
Ferrous Gluconate—See PF Vol. 29 No. 3, page 630.
Ferumoxides Injection—See PF Vol. 28 No. 3, page 758.
Fexofenadine Hydrochloride—See PF Vol. 28 No. 6, page 1790.
Fexofenadine Hydrochloride Capsules—See PF Vol. 29 No. 4, page 1027.
Finasteride Tablets—See PF Vol. 29 No. 2, page 403.
Flumazenil—See PF Vol. 29 No. 5, page 1480.
Flumazenil Injection—See PF Vol. 29 No. 5, page 1484.
Fluoxetine Delayed-Release Capsules—See PF Vol. 29 No. 5, page 1486.
Flutamide—See PF Vol. 29 No. 5, page 1488.
Flutamide Capsules—See PF Vol. 29 No. 5, page 1490.
Fluvastatin Capsules—See PF Vol. 25 No. 4, page 8423.
Folic Acid Tablets—See PF Vol. 29 No. 2, page 409.
Fosphenytoin Sodium—See PF Vol. 29 No. 5, page 1492.
Fosphenytoin Sodium Injection—See PF Vol. 29 No. 5, page 1493.
Fructose—See PF Vol. 29 No. 5, page 1496.
Furosemide—See PF Vol. 29 No. 5, page 1497.
Gabapentin—See PF Vol. 29 No. 1, page 72.
Gabapentin Capsules—See PF Vol. 28 No. 2, page 298.
Gadoversetamide—See PF Vol. 29 No. 5, page 1497.
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Minerals Tablets—See PF Vol. 28 No. 5, page 1543.
Nettle—See PF Vol. 29 No. 4, page 1285.
Powdered Nettle—See PF Vol. 29 No. 4, page 1289.
Powdered Nettle Extract—See PF Vol. 29 No. 4, page 1289.
Oil- and Water-Soluble Vitamins Tablets—See PF Vol. 28 No. 5, page 1544.
Oil- and Water-Soluble Vitamins with Minerals Capsules—See PF Vol. 28 No. 5, page 1544.
Oil- and Water-Soluble Vitamins with Minerals Tablets—See PF Vol. 29 No. 2, page 510.
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Saw Palmetto Capsules—See PF Vol. 29 No. 4, page 1291.
Saw Palmetto Extract—See PF Vol. 26 No. 6, page 1567.
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Valerian Capsules—See PF Vol. 27 No. 1, page 1825.
Water-Soluble Vitamins with Minerals Capsules—See PF Vol. 28 No. 5, page 1547.
Water-Soluble Vitamins with Minerals Tablets—See PF Vol. 28 No. 5, page 1548.

GENERAL NOTICES AND REQUIREMENTS

"Official" and "Official Articles"—See PF Vol. 28 No. 1, page 88.

NF MONOGRAPHS

Alfadex—See PF Vol. 29 No. 4, page 1092.
Amminio Methacrylate Copolymer Dispersion—See PF Vol. 28 No. 2, page 628.
Ammonium Sulfate—See PF Vol. 29 No. 1, page 136.
Aspartame Acesulfame—See PF Vol. 29 No. 2, page 453.
Benzyl Alcohol—See PF Vol. 29 No. 5, page 1598.
Butylparaben—See PF Vol. 29 No. 5, page 1598.
Candelilla Wax—See PF Vol. 29 No. 1, page 138.
Caprylocaproyl Macrogolglycerides—See PF Vol. 29 No. 3, page 688.
Carbomer Copolymer—See PF Vol. 29 No. 3, page 691.
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Carboxymethylcellulose Calcium—See PF Vol. 23 No. 6, page 5063.
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Cellulose Acetate Butyrate—See PF Vol. 25 No. 2, page 7861.
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Cottonseed Oil, Hydrogenated—See PF Vol. 29 No. 1, page 141.
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Lauroyl Macrogolglycerides—See PF Vol. 26 No. 2, page 456.
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Magnesium Stearate—See PF Vol. 29 No. 2, page 474.
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Mono- and Di-glycerides—See PF Vol. 29 No. 5, page 1600.
Oleic Acid—See PF Vol. 29 No. 3, page 701.
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Oral Solution Vehicle—See PF Vol. 29 No. 4, page 1114.
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Compound Orange Spirit—See PF Vol. 28 No. 5, page 1466.
Peanut Oil—See PF Vol. 29 No. 4, page 1117.
Phenolsulfonphthalein—See PF Vol. 28 No. 6, page 1899.
2-Phenoxyethanol—See PF Vol. 28 No. 6, page 1900.
Polyethylene Glycol—See PF Vol. 29 No. 3, page 702.
Polyethylene Glycol Ointment—See PF Vol. 29 No. 3, page 702.
Polyisobutylene—See PF Vol. 29 No. 1, page 150.
Polyoxyl Lauryl Ether—See PF Vol. 29 No. 4, page 1117.
Polyoxyl Stearyl Ether—See PF Vol. 29 No. 4, page 1118.
Polyoxyl Oleate—See PF Vol. 29 No. 4, page 1121.
Propylene Glycol Monostearate—See PF Vol. 29 No. 2, page 479.
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Sodium Cetostearyl Sulfate—See PF Vol. 29 No. 4, page 1122.
Sorbitol—See PF Vol. 29 No. 4, page 1125.
Anhydrized Liquid Sorbitol—See PF Vol. 29 No. 4, page 1128.
Sorbitol Solution—See PF Vol. 28 No. 3, page 787.
Noncrystallizing Sorbitol Solution—See PF Vol. 29 No. 4, page 1130.
Soybean Oil—See PF Vol. 29 No. 3, page 668.
Hydrogenated Soybean Oil—See PF Vol. 29 No. 3, page 704.
Starch—See PF Vol. 29 No. 3, page 705.
Modified Starch—See PF Vol. 29 No. 4, page 1132.
Pregelatinized Starch—See PF Vol. 29 No. 5, page 1600.
Pregelatinized Modified Starch—See PF Vol. 29 No. 4, page 1133.
Tapioca Starch—See PF Vol. 29 No. 4, page 1134.
Stearic Acid—See PF Vol. 29 No. 2, page 480.
Purified Stearic Acid—See PF Vol. 29 No. 3, page 706.
Stearoyl Macrogolglycerides—See PF Vol. 29 No. 4, page 1135.
Sunflower Oil—See PF Vol. 27 No. 4, page 2803.
Talc—See PF Vol. 29 No. 1, page 157.
Tobramycin Inhalation Solution—See PF Vol. 28 No. 3, page 789.
Tolu Balsam Syrup—See PF Vol. 28 No. 5, page 1467.
Tolu Balsam Tincture—See PF Vol. 28 No. 5, page 1468.
Tribasic Sodium Phosphate—See PF Vol. 29 No. 1, page 162.
Medium-Chain Triglycerides—See PF Vol. 29 No. 2, page 475.

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled

(Canceled proposals may be republished at any time in a future number of *Pharmacopeial Forum*.)

[*PF* 29(1)–*PF* 29(6)]

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
General Notices			
Preservation, Packaging, Storage, and Labeling	26	3	653
USP Monographs			
†Acepromazine Maleate—*Packaging and storage*	27	3	2493
†Acyclovir—*Packaging and storage*	29	3	602
Amoxicillin and Clavulanate Potassium for Oral Suspension—*Water*	28	5	1390
†Antivenin (Crotalidae) Polyvalent	28	4	1068
Bacitracin—*Identification*	28	3	745
Cabergoline (new)	24	6	7141
Cabergoline Tablets (new)	24	6	7142
Carbon Dioxide—*Air*, *Assay*	28	4	1082
Carboxymethylcellulose Sodium—*Harmonization* (entire submission)	26	5	1403
Cefuroxime Axetil Tablets—*Dissolution Test 2*	27	2	2128
Desonide (new)	22	3	2275
Desonide Cream (new)	22	3	2276
Desonide Ointment (new)	22	3	2277
Dihydroergotamine Mesylate (entire submission)	24	1	5562
Dihydroergotamine Mesylate Injection—*Chromatographic purity*, *Assay*	24	1	5564
Enalaprilat Injection (new)	19	4	5587
Enoxaparin Sodium (new)	22	6	3031
Enoxaparin Sodium Injection (new)	22	6	3038
Epinephryl Borate Ophthalmic Solution—*USP Reference standards*, *Assay*	23	3	3991
Fluoxetine Capsules—*Chromatographic purity*, *Related compounds*, *Assay*	27	2	2150
Gabapentin (new)	27	5	3004
†Ganciclovir—*Packaging and storage*	29	3	630
Hydrocodone Bitartrate and Acetaminophen Tablets—*Labeling, Dissolution*	27	6	3301
Ketamine Hydrochloride—*Assay*	28	4	1140
Levonorgestrel—*Limit of ethylsecothindrone*	27	3	2565
Mecamylamine Hydrochloride (entire submission)	28	2	320
Hydroxypropyl Methylcellulose—*Harmonization* (new)	24	5	6726
Methylcellulose—*Harmonization* (new)	24	5	6737
Methylprednisolone Acetate for Rectal Suspension—*Packaging and storage*	27	1	1803
Miconazole Nitrate Cream—*Assay*	26	5	1302
Minocycline Hydrochloride—*Chromatographic purity, Assay*	28	3	770
Montelukast Sodium (new)	24	6	7160
Montelukast Sodium Tablets (new)	24	6	7162
Morphine Sulfate Extended-Release Capsules (new)	25	4	8426
Nitrofurantoin Extended-Release Capsules (new)	25	5	8853
Ondansetron Hydrochloride—*Limit of ondansetron related compound D*	29	1	92
Oxybutynin Chloride—*Chromatographic purity*	26	6	1561
Perflutren Protein-Type A Microspheres for Injection [Former title: Albumin Encapsulated Octafluoropropane Microspheres for Injection] (new)	27	4	2769
Povidone (entire submission)	22	6	3163
Sertraline Hydrochloride (new)	24	6	7179
Sertraline Hydrochloride Tablets (new)	24	6	7181
†Sodium Bicarbonate—*Heavy metals*	28	5	1446
Somatropin (new)	25	4	8540
Somatropin for Injection (new)	25	4	8551
†Sulfasalazine Delayed-Release Tablets—*Disintegration*	28	3	788
Sulindac—*Chromatographic purity*	25	5	8879
Sulindac Tablets	25	5	8880
Sunflower Oil—*Briefing*	27	4	2779
Sutilains (new)	27	2	2199

Proposed Revisions and New Text Previously Presented in *PF* but Now Canceled *(continued)*

Title and Proposal	*PF Volume, Issue, and Page Numbers of Canceled Proposals* *Vol.*	*No.*	*Page(s)*
Sutilains Ointment (new)	27	2	2201
†Tetanus Toxoid	28	4	1194
Titanium Dioxide (new)	24	2	5796
Vancomycin—*Chromatographic purity*, *Labeling*	27	4	2783
Vancomycin Hydrochloride—*Labeling*, *Other requirements*	27	4	2784
Vancomycin Injection—*Chromatographic purity*	27	4	2784
Vancomycin Hydrochloride for Injection—*Chromatographic purity*	27	4	2786
Vancomycin for Injection (entire submission)	27	4	2785
Sterile Vancomycin Hydrochloride—*Title*	27	4	2786
Sterile Water for Injection—*pH*, *Other requirements*	27	4	2787
Sterile Purified Water	28	4	1272
USP General Test Chapters			
⟨11⟩ USP Reference Standards			
USP Gabapentin Related Compound C RS	25	6	9222
†*USP Flumazenil RS*	29	5	1602
USP Nabumetone Alcohol RS	25	6	9222
USP Oxybutynin Chloride Related Compound A RS	26	6	1606
USP Paroxetine Related Compound D RS	25	3	8222
USP Povidone RS	20	5	8060
†*USP Sodium Starch Glycolate RS*	22	6	3212
USP Sulindac Related Compound A RS	25	5	8893
⟨41⟩ Weights and Balances (entire submission)	26	6	1607
⟨61⟩ Microbial Limit Tests—*Harmonization*	27	2	2299
⟨62⟩ Microbiological Procedures for Absence of Objectionable Microorganisms—*Harmonization*	27	2	2313
⟨71⟩ Sterility Tests (entire submission)	26	4	1102
⟨581⟩ Vitamin D Assay—*Biological method*	26	4	1111
†⟨643⟩ Total Organic Carbon (entire submission)	28	4	1232
⟨661⟩ Containers—*Polypropylene Containers* (added)	26	4	1117
⟨786⟩ Particle Size Distribution Estimation by Analytical Sieving—*Harmonization*	25	1	7460
USP General Information Chapters			
⟨1010⟩ Analytical Data—Interpretation and Treatment	27	5	3086
⟨1151⟩ Pharmaceutical Dosage Forms—*Stability*	26	2	499
⟨1186⟩ Shipping and Storage of Labile Preparations	28	2	495
Dietary Supplements Monographs			
Asian Ginseng Capsules (new)	26	3	775
Saw Palmetto Capsules—*Disintegration and dissolution*	26	6	1571
NF Monographs			
†Ammonium Sulfate (new)—*Labeling, USP Reference standards*	29	1	136
Benzyl Alcohol (entire submissions)	27	4	2790, 2855
Cellulose Acetate	23	5	4677
†Cetrimonium Bromide (new)—*Labeling*	29	1	139
Dimethicone—*Bacterial endotoxins*	28	3	813
Hydroxyethyl Cellulose (entire submission)	20	6	8311
Hydroxypropyl Beta Cyclodextrin (new)	24	6	7284
Silicon Dioxide (entire submission)	24	6	7191
Colloidal Silicon Dioxide—*Harmonization*	24	6	7187, 7194
Sodium Starch Glycolate (entire submission)	22	6	3202
Rice Starch (new)	23	4	4348
Stearic Acid—*Harmonization*	20	6	8313
	28	2	583
Sucrose (entire submission)	22	6	3206
Reagents, Indicators, and Solutions			
0.5 M Copper Sulfate Solution (new)	26	5	1382
Cyclohexylmethanol (new)	25	1	7582
Dicyclohexyl (new)	25	1	7582
17α-Estradiol (new)	27	2	2278
Ethylbenzene (new)	25	1	7582
†Hexamethylenetetramine (new)	28	3	850
2-Isopropylphenol (new)	27	4	2838
Reagent Footnotes			
Footnote 108	29	2	508

†New cancellations in 29(6).

HARMONIZATION

This section contains monographs or chapters undergoing harmonization by the Pharmacopeial Discussion Group (PDG). The PDG consists of the United States Pharmacopeia (USP), the European Pharmacopoeia (EP), and the Japanese Pharmacopoeia (JP). The process of harmonization is composed of several steps **(*Stages*)**.

Stage 1: Identification The PDG identifies items to be harmonized and designates a coordinating pharmacopeia for each item. The PDG distributes the work by consensus among the three participating pharmacopeias. Harmonization may be carried out retrospectively for existing monographs or chapters, or prospectively for new monographs or chapters.

Stage 2: Investigation The investigation process conducted by the coordinating pharmacopeia results in the preparation of a Stage 3 draft monograph or chapter accompanied by a report giving the rationale for the proposal and including validation data where appropriate. This report is based on input that comes from users, authorities, producers, associations, literature, experts, and staff.

Stage 3: Proposal The Stage 3 draft is reviewed and commented on by the other two pharmacopeias. The coordinating pharmacopeia reviews those comments, prepares a harmonized Stage 4 draft, and sends it to the other two participating pharmacopeias.

Stage 4: Official Inquiry The Stage 4 draft is published in the Forum of each pharmacopeia. In *PF*, this stage appears as OFFICIAL INQUIRY STAGE 4 in the *Harmonization* section. Each pharmacopeia analyzes the comments it receives and submits the consolidated comments to the coordinating pharmacopeia, which then reviews those comments, prepares a harmonized Stage 5A draft, and sends it to the other two participating pharmacopeias.

Stage 5: Consensus

A. Provisional

The Stage 5A draft is reviewed and commented on by the other two pharmacopeias. When consensus is reached, a CONSENSUS STAGE 5B document is prepared by the coordinating pharmacopeia.

B. Final

The Stage 5B draft (consensus document) is sent by the coordinating pharmacopeia to the other two participating pharmacopeias for final approval.

Stage 6: Adoption Each pharmacopeia incorporates the harmonized Stage 5B draft according to its own procedure. Adopted items are published by the three pharmacopeias in their Supplements or, where applicable, in a new edition of their Pharmacopeias.

Stage 7: Date of Implementation The pharmacopeias inform each other of the date of implementation in the particular region.

PHARMACOPEIAL PREVIEWS

This section contains potential revisions not yet targeted for official adoption. These may include drafts for new monographs or chapters; drafts for standards that would require new or unusual technology; drafts for which more data are required; or changes that would affect numerous monographs, thus having a broad impact on individual products. Readers should review the drafts in this section and provide comments to the appropriate staff liaison whose name is cited in the Briefing (use the *Staff Directory* to find the contact information).

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

BRIEFING

Name of Item, citations of the most recent USP publications in which this item appeared. Rationale for the revision. Other relevant information. (For example, if a chromatographic method is being used, column specifications and retention times for compounds of interest.) Finally, the Committee designation (see *How To Use PF*), the name of the scientific staff liaison who handled this item, and the USP tracking correspondence number, as shown in the example below:

(PA5: K. Russo) RTS—55678-1

Symbols No symbols are used in this section, as Previews are not yet targeted for official adoption.

DIETARY SUPPLEMENTS—MONOGRAPHS

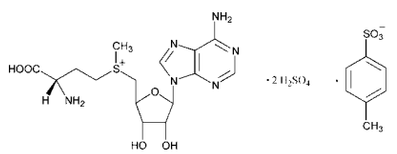
BRIEFING

***S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate.** Because there is no existing *USP* monograph for this dietary supplement, a new monograph is being previewed. The liquid chromatographic procedures in the *Assay, Content of p-toluene sulfonic acid,* and *Related compounds* test are based on analyses performed using a Supelco Supelcosil LC-SCX brand of L9 column. The retention time of the *S*-adenosyl-L-methionine ion is about 4.7 minutes. The liquid chromatographic procedures in the *Isomeric ratio* determination are based on analyses performed using a YMC C18 brand of L1 column. The retention times of the *R,S*- and *S,S*-isomers are about 17.4 and 18.5 minutes, respectively. The liquid chromatographic procedures in the *Content of sulfate* determination are based on analyses performed using a Dionex Ion Pac AS14A brand of L46 column. The retention time of sulfate is about 12.7 minutes. The name of this monograph has been assigned as a temporary working title. The Expert Committee on Nomenclature and Labeling will be considering establishing a shorter, useful name to be used as the official title for this monograph. Suggestions from reviewers of *PF* will be welcomed in that regard.

(DSN: L. Evans) RTS—40057-1; 40057-2; 40057-3; 40057-4; 40057-5; 40057-6; 40057-7

Add the following:

S-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate



$C_{22}H_{34}N_6O_{16}S_4$ 766.56

S-(Adenosyl)-L-methionine disulfate *p*-toluene sulfonate.

(3*S*)-5′-[(3-Amino-3-carboxypropyl)methylsulfonio]-5′-deoxyadenosine hydroxide, disulphate-methylbenesulfonate.

(3*S*)-5′-[(3-Amino-3-carboxypropyl)methylsulfonio]-5′-deoxyadenosine inner salt [*29908-08-0*].

» *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate contains not less than 49.5 percent and not more than 53.0 percent of *S*-adenosyl-L-methionine ($C_{15}H_{23}N_6O_5S^+$), not less than 21.0 percent and not more than 24.0 percent of *p*-toluene sulfonate as *p*-toluene sulfonic acid ($C_7H_7N_6O_3S$) and not less than 23.5 percent and not more than 26.5 percent of sulfate and the sum of *S*-adenosyl-L-methionine, *p*-toluene sulfonate, and sulfate is not less than 95.0 percent on the dried basis.

Packaging and storage—Preserve in tight, light-resistant containers, and store in a refrigerator.

USP Reference standards ⟨11⟩—*USP S-Adenosyl-L-Methionine Disulfate p-Toluene Sulfonate RS.*

Identification—

A: *Infrared Absorption* ⟨197K⟩.

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

pH ⟨791⟩: between 1.0 and 2.0 , in an aqueous solution (1 in 20).

Water, *Method Ia* ⟨921⟩: not more than 2.0%.

Heavy metals, *Method I* ⟨231⟩: not more than 0.002%.

Organic volatile impurities, *Method V* ⟨467⟩: not more than 0.001%.

Isomeric ratio—

Buffer A—Transfer 4.2 g of citric acid monohydrate, 2.03 g sodium dihydrogen phosphate dihydrate to a 1-L volumetric flask, dissolve in and dilute with water to volume, and mix.

Mobile phase—Transfer 4.0 g of sodium dodecyl sulfate and 440 mL of acetonitrile to a 1-L volumetric flask, dilute with *Buffer A* to volume, and mix.

Standard solution and *Test solution*—Use the *Standard preparation* and the *Assay preparation,* prepared as directed in the *Assay.*

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 254-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L1. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard solution,* and record the peak response as directed for *Procedure:* the resolution, *R,* between *S,S*-isomer and *R,S*-isomer is not less than 1.0; and the relative retention times are about 0.94 and 1.0 for *S,S*-isomer and *R,S*-isomer, respectively.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the peak responses. Identify the peaks of *S,S*- and *R,S*-isomers in the chromatogram of the *Test solution* by comparison with the chromatogram of the *Standard solution,* and calculate the percentage of *S,S*-isomer by the formula:

$$100[r_{SS} / (r_{SS} + r_{RS})],$$

in which r_{SS} and r_{RS} are the areas of the peaks corresponding to the *S,S*-isomer and *R,S*-isomer, respectively, in the *Test solution*. Not less than 75% of *S,S*-isomer is found.

Related compounds—

Mobile phase—Prepare as directed under *Assay.*

Test solution—Use the *Assay preparations* under *Assay.*

Chromatographic system —Prepare as directed under *Assay.* Chromatograph the *Standard preparation,* and record the peak responses as directed for *Procedure.*

Procedure—Inject a volume (about 20 µL) of the *Test solution* into the chromatograph, record the chromatogram, and measure the peak responses. Calculate the percentage of adenosine, *S*-adenosyl-L-homocysteine, methylthioadenosine, and any other impurity in the portion of *S*-Adenosyl-L-Methionine Disulfate *p*-Toluenesulfonate taken by the formula:

$$100(r_i / r_s),$$

in which r_i is the peak area for each individual impurity; r_s is the sum of the peak areas of all the peaks.

Name	Relative Retention Time	Limit (%)
Adenosine	about 0.86	1.0
S-Adenosyl-L-homocysteine	about 0.90	1.0
Methylthioadenosine	about 2.06	1.5
Other individual impurities	—	0.1
Total impurities	—	3.5

Content of sulfate—

Mobile phase—Prepare a solution of 8.0 mM sodium carbonate and 1.0 mM sodium bicarbonate in water.

Standard solution—Dissolve an accurately weighed quantity of potassium sulfate in water, to obtain a solution having a known sulfate concentration of about 0.18 mg per mL.

Test solution—Transfer about 50 mg of *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with an ion detector with suppressed conductivity, a 4.0-mm × 25-cm column that contains 7-µm packing L46. The column temperature is maintained at 30°. The flow rate is about 1 mL per minute. Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the column efficiency

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is not less than 8200 theoretical plates; the tailing factor is not more than 1.1; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the sulfate peak. Calculate the percentage of sulfate in the portion of the *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate taken by the formula:

$$10{,}000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of the *Standard solution; W* is the weight, in mg, of *S*-adenosyl-L-methionine disulfate *p*-toluene sulfonate taken to prepare the *Test solution;* and r_U and r_S are the peak responses obtained for sulfate in the chromatograms of the *Test solution* and the *Standard solution,* respectively.

Content of *p*-toluene sulfonic acid—

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

Standard solution—Dissolve an accurately weighed quantity of *p*-toluene sulfonic acid monohydrate in water, to obtain a solution having a known concentration of about 0.5 mg per mL.

Test solution—Transfer about 100 mg of *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system—Prepare as directed in the *Assay.* Chromatograph the *Standard solution,* and record the peak responses as directed for *Procedure:* the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas of the *p*-toluene sulfonic acid peak. Calculate the percentage of *p*-toluene sulfonic acid in the portion of the *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate taken by the formula:

$$10{,}000(C/W)(r_U/r_S),$$

in which C is the concentration, in mg per mL, of the *Standard solution; W* is the weight, in mg, of *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate taken to prepare the *Test solution;* and r_U and r_S are the peak responses obtained for *p*-toluene sulfonic acid in the chromatograms of the *Test solution* and the *Standard solution,* respectively.

Assay—

Mobile phase—Prepare a filtered and degassed solution of 0.5 M ammonium formate in water, and adjust with formic acid to a pH of 4.0. Make adjustments if necessary (see *System Suitability* under *Chromatography* ⟨621⟩).

Standard preparation—Dissolve an accurately weighed quantity of USP *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate RS in water, to obtain a solution having a known concentration of about 1.0 mg per mL.

Assay preparation—Transfer about 100 mg of *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate, accurately weighed, to a 100-mL volumetric flask, dissolve in and dilute with water to volume, and mix.

Chromatographic system (see *Chromatography* ⟨621⟩)—The liquid chromatograph is equipped with a 260-nm detector and a 4.6-mm × 25-cm column that contains 5-µm packing L9. The flow rate is about 1.2 mL per minute. Chromatograph the *Standard preparation,* and record the peak response as directed for *Procedure:* the column efficiency is not less than 3950 theoretical plates; the tailing factor is not more than 1.7; and the relative standard deviation for replicate injections is not more than 1.0%.

Procedure—Separately inject equal volumes (about 20 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and

measure the area of the major peak. Calculate the quantity, in mg, of $C_{15}H_{23}N_6O_5S$ in the portion of the *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate taken by the formula:

$$(399.28/766.56)100C(r_U/r_S),$$

in which 399.28 and 766.8 are the molecular weights of *S*-adenosyl-L-methionine and *S*-adenosyl-L-methionine disulfate *p*-toluene sulfonate, respectively; *C* is the concentration, in mg per mL, of USP *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained for *S*-adenosyl-L-methionine in the chromatograms of the *Assay preparation* and the *Standard preparation,* respectively.

⟨11⟩ **USP Reference Standards**

Add the following:

USP *S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate RS—Do not dry; determine the water content titrimetrically at time of use. Keep container tightly closed. Protect from light, and store in a refrigerator.

Description and Solubility

Add the following:

***S*-Adenosyl-L-Methionine Disulfate *p*-Toluene Sulfonate:** White powder. Freely soluble in water.

STIMULI TO THE REVISION PROCESS

This section may contain the following:
- reports or statements of authoritative committees
- original research reports
- evaluations of new and existing pharmacopeial methods
- commentaries
- articles relevant to compendial issues

These items are published to stimulate discussion and continual review of Pharmacopeial standards. Generally, if an Expert Committee publishes an article on which they are specifically seeking comment, this will be clearly stated in the article. Readers may submit comments on issues raised in this section, but comment is not as critical as that for the *In-Process Revision* and *Pharmacopeial Previews* sections. Readers interested in submitting comments should see *Instructions to Authors.*

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Applications of Ion Chromatography in Pharmaceutical and Drug Analysis

Shreekant Karmarkar* and Dennis Jenke

ABSTRACT Since its introduction in 1975, ion chromatography (IC) has developed and matured into an important analytical methodology in a number of diverse applications and industries. This article briefly describes IC principles and instruments and also provides a review of IC applications developed and validated for the determination of active and inactive ingredients, excipients, degradation products, and impurities relevant to pharmaceutical analyses. Although at present IC-based procedures are cited only in a handful of USP monographs, this article shows that many more IC methods have been successfully developed and validated for pharmaceutical and drug analysis.

INTRODUCTION

Since its introduction in 1975 (*1*), ion chromatography (IC) has developed and matured into an important analytical methodology in a number of diverse applications and industries. The technique, a type of high-performance liquid chromatography (HPLC), has gained popularity in laboratories for the analysis of inorganic anions and cations, organic acids, carbohydrates, sugar alcohols, aminoglycosides, amino acids, proteins, and glycoproteins in environmental, agricultural, pharmaceutical, biotechnology, metal plating, power generation, semiconductor fabrication, and industrial samples. Several books and chapters on IC furnish a detailed review of IC principles and instruments (*2–4*). This article briefly describes IC principles and instruments and also provides a review of IC applications for the determinations of active and inactive ingredients, excipients, degradation products, and impurities relevant to pharmaceutical and drug analyses. Although not reviewed in the present article, IC is extensively used in the biotechnology industry for the determinations of amino acids, peptides, proteins, glycoproteins, carbohydrates, etc. [For the application of IC in amino acid analysis, see *Pharmacopeial Forum* 29(5), "A New Technique for Amino Acid Analysis in Pharmaceutical Samples."]

The IC instrument closely resembles conventional HPLC instrumentation. Typical components of an IC system (*Figure 1*) include an optional autosampler, a high-pressure pump, an injection valve with a sample loop of suitable size (typically 10 to 250 µL), a guard column, an analytical column, a suppressor or other form of postcolumn reaction system, a flow-through detector, and a data system ranging in complexity from a chart recorder to a computerized data system. Typically all of the components in contact with the eluent and sample are made from inert materials such as PEEK (polyetheretherketone), although a conventional HPLC system also may be used provided the materials are compatible with the mobile phase used and injected samples. Following suitable sample preparation, the sample is introduced to the IC via the injection valve. The ions are separated based on various modes such as ion exchange, ion exclusion, or ion pair. After optional chemical suppression or other postcolumn reaction on the column effluent, the ions are detected using conductivity, pulsed amperometry, or other detection modes. The IC setup, therefore, is very similar to that of HPLC. A comparison of IC and HPLC is presented in *Table 1,* which shows that IC differs from HPLC in several regards: First, ions are separated in IC with partial impact of hydrophobic characters of the ionic analytes. Second, due to the nature of the separation, ionic mobile phases are used that are not transparent to typical conductometric detection. Third, the ionic mobile phases quite often necessitate use of a suppressor prior to conductometric detection, although nonsuppressed conductometric detection, pulsed amperometric detection, direct or indirect UV detection, or other forms of detection have been successfully used in pharmaceutical analysis.

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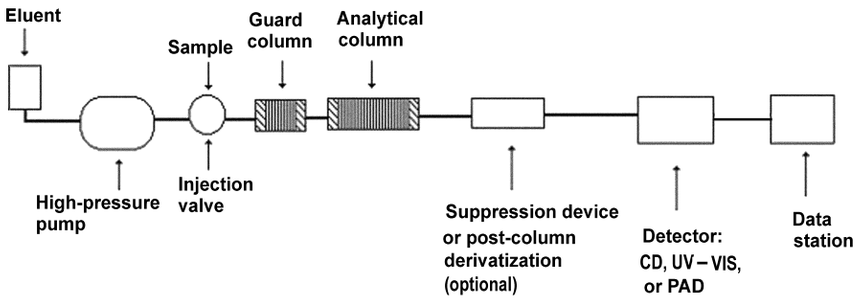

Fig. 1. Components of a typical IC system illustrated schematically. CD, conductivity; PAD, pulsed amperometric detection.

IC is a complementary technique to the more commonly used reversed-phase and normal-phase HPLC and to atomic absorption (AA) and inductively-coupled plasma (ICP) techniques in pharmaceutical analysis. At present IC-based procedures are cited only in a handful of USP monographs (*Table 2*), although many more IC methods have been successfully developed and validated (*Tables 6–10*).

EXPERIMENTAL PROCEDURES

Stationary and Mobile Phases

A survey of IC columns is presented in *Tables 3* and *4*. As IC has developed and matured, the number of ion-exchange materials developed for IC has increased tremendously, facilitated by the understanding of the processes taking place at the surface of the stationary phase. In contrast to the silica-based column packing prevalent in classical HPLC, organic polymers are predominantly used as support materials for IC. Such materials have a higher stability with respect to extremes in pH and in many cases are fully compatible with organic solvents.

The stationary phases used in IC differ in terms of both the support material used and in terms of the different pore sizes and ion-exchange capacities. Although ion exchangers with relatively high exchange capacities are used in cation applications, stationary phases used in anion applications typically have low ion-exchange capacities, thereby facilitating conductivity detection.

Recently, Weiss and Jensen have published a compilation of stationary phases used in modern IC (*6*). Information in this reference is summarized and augmented in *Tables 3* and *4*. A scheme of the selection criteria for separation and detection of ions is presented on page 9 of the book on IC by Weiss (*2*). Column selection guides are also available from several companies, e.g., Alltech, Dionex, Hamilton, Shodex, and Transgenomic.

Because the dominant separation mechanism in IC is ion exchange, the mobile phase consists of mono- or divalent ionic species to accomplish the separation. In ion-exclusion methods, particularly of organic acids, the mobile phase consists of mineral acids in order to maintain organic acids in their undissociated forms. Often, the detection mode to be used dictates the mobile phase employed for the separation of ionic species, and as such the typical mobile phases used in IC are described in the section on IC detection.

IC with Suppressed or Nonsuppressed Conductivity Detection

As a universal method for the detection of ionic species, conductivity detection is, by far, the most commonly employed mode of detection in IC. In the early 1970s, the crucial milestones accomplished by scientists at Dow Chemicals (*1*) in their original IC development work included development of low-capacity ion-exchange resins for efficient chromatographic separation and conductometric detection of ions in chemically suppressed mobile phase.

In suppressed IC, the background conductance of the ionic mobile phase is significantly reduced as it flows through the suppression device. For example, dilute NaOH, ~10–50 mM used as mobile phase in IC of anions is converted to H_2O when the column effluent containing NaOH flows through a suppressor device present in H^+ form. The analyte ionic species in the column effluent, on the other hand, are converted from their Na form to highly conducting acid forms. The reduced background conductance and the enhanced signal of the ionic species result in increased sensitivity for the conductometric detection of ions in suppressed IC. Further details of chemical suppression in IC can be found in various books and chapters on IC (*2–4*). The chemical suppression devices in common use today essentially fall into two broad categories: In the first type the reactions occur across an ion-exchange membrane (*7*). In the second

type the suppression reactions occur in a packed bed of high-exchange-capacity resin material (*8, 9*). In a third type, although not commonly used, the suppression reactions occur as the eluent stream mixes with the flowing stream of high-capacity resin material (*10*). The suppressed conductometric detection is employed in environmental methods, regulated by US EPA and other agencies, and for detection of trace ions in high-purity waters. The commonly used mobile phases in IC of anions include mixtures of bicarbonate, carbonate, and hydroxide, and in IC of cations methane sulfonic acid is typically used.

Soon after the introduction of IC technology, Gjerde et al. in 1979 developed IC without chemical suppression, in which the analytical column effluent flows directly to a conductivity detector (*11*). The typical eluents used in nonsuppressed IC are phthalic acid and *p*-hydroxybenzoic acid for the determination of anions, and methanesulfonic acid for the determination of cations. The equivalent conductance values of chloride, sulfate, and other common anions are significantly greater than those of the eluent anions, and hence positive peaks are detected as the anions are carried through the detector. The equivalent conductance values of sodium, potassium, and other common cations are appreciably smaller than those of the eluent cations, and hence negative peaks are detected as the cations are carried through the detector.

Nonsuppressed IC is easier to operate, and it is a useful technique for determining ions of weak acids such as cyanide and sulfide that do not conduct after chemical suppression. Pharmaceutical analyses can be performed in nonsuppressed mode because the quantitation limits are usually in upper mg/L to low percentage levels. Although suppressor-based methodologies often must be implemented on instrument systems specifically designed for this purpose, it is possible to perform IC without the suppressor on existing HPLC instrumentation. A consideration of the ability to perform IC analyses on various commercially available HPLC systems (e.g., systems from Agilent, Waters, and Shimadzu) is presented in *Table 5*. As this table indicates, it is possible to perform IC analysis on such HPLC instruments because the commonly used eluents in IC include dilute concentrations of bases and acids that are compatible for use on the existing HPLC instruments. It is, however, prudent to consult the instrument manufacturer regarding applicability of the instrument for the IC analysis.

Other Detectors

Other detectors commonly used in IC include pulsed amperometry, direct UV detection, or postcolumn derivatization followed by UV–VIS detection.

Pulsed amperometric detection (PAD) is commonly used for the detection of electroactive ions, e.g., organic compounds such as carbohydrates, sugar alcohols, amino acids, and organic sulfur species. In PAD, organic molecules are detected by an oxidative desorption process at the surface of an electrode located in the column effluent stream. Following the detection process, a series of potentials are applied for fixed time periods to clean the electrode surface. Compared with conventional amperometry, a rapidly repeating sequence of different working potentials in PAD, referred to as a waveform, helps in removal of oxidizable and reducible species from the electrode surface. A review of the waveforms employed for detection and electrode cleaning is presented in Dionex's technical note 21 (*79*).

Several inorganic and organic ions possess a UV chromophore. Direct UV detection is used for such ions, e.g., organic acids, bromide, iodide, nitrate, nitrite, thiosulfate, and cyanometalic complexes. Analogous to the inverse conductometric detection of cations, UV detection may also be performed indirectly. This method is called indirect photometric chromatography (IPC). Examples of IPC for inorganic and organic ions are listed in *Table 7*.

In photometric detection, column effluent is derivatized with a color-forming reagent prior to detection in VIS wavelength. A classic example is the detection of metal ions (*Table 6*) in which the column effluent is derivatized with 4-(2-pyridylazo)-resorcinol and detection is performed at 510–530 nm.

Sample Preparation

Typically, sample preparation in IC includes only dilution or filtering through a 0.45-µm filter or both. Certain samples may require removal of undesirable species by pushing the sample through solid-phase extraction (SPE) cartridges containing, depending on the application, different packing materials. For example, a highly alkaline sample can be neutralized by pushing it through an SPE cartridge packed with cation-exchange material in H^+ form. Further details on SPE procedures can be found in reference 2.

APPLICATIONS OF IC IN PHARMACEUTICAL AND DRUG ANALYSIS

As dictated by the nature of the analyte, IC has been applied to all aspects of the manufacturing and disposition of pharmaceutical products, including the characterization of drug substances and active ingredients, excipients, and other so-called inert product components, degradation products, and/or impurities and process streams. The following sample types are analyzed: raw materials, intermediates (including media and culture broths), bulk active ingredients, diluents, formulated products, production equipment cleaning solutions, and waste streams. The method is especially valuable in the pharmaceutical industry for ionic analytes (in products containing non-ionic components) that have little or no native UV absorbance. *Figure 2* shows a chromatogram for the determination of inorganic cations in electrolyte solution with a runtime of less than 10 minutes. However, the ability to couple the ion-exchange separation with numerous detection strategies, e.g., PAD, expands IC applications to instances were analyte-specific detection strategies can provide the required degree of sensitivity and/or specificity. High-performance anion-exchange

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chromatography, coupled with PAD, is illustrated in *Figure 3* for the determinations of carbohydrates, alditols, alcohols, and glycols (*78*). Utilization of such strategies allows IC applications to be implemented on appropriately configured HPLC systems. Additionally, ion-exclusion separations expand the range of application of IC to aliphatic organic acids (*Figure 4*) as well as to non-ionic analytes of significant pharmaceutical interest, including alcohols and carbohydrates. The wide dynamic range of the methodology makes it applicable for the quantitation of trace contaminants as well as major product components.

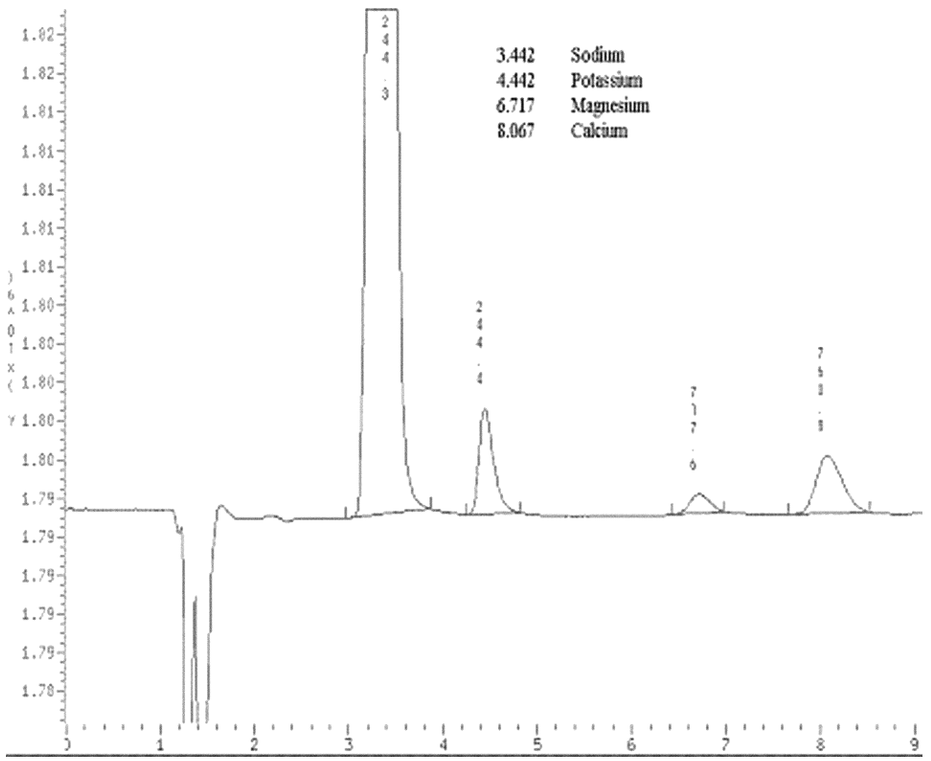

Fig. 2. Chromatogram illustrating separation of cations in electrolyte solution. IC conditions: WATERS IC Pak CM/D column, 3.9 × 150 mm at 30 °C, 4.0 mM HNO_3 eluent at 1.0 mL/min, 20 µL injection, ALLTECH conductivity detector at 35 °C with 100 µS sensitivity, and inverse polarity.

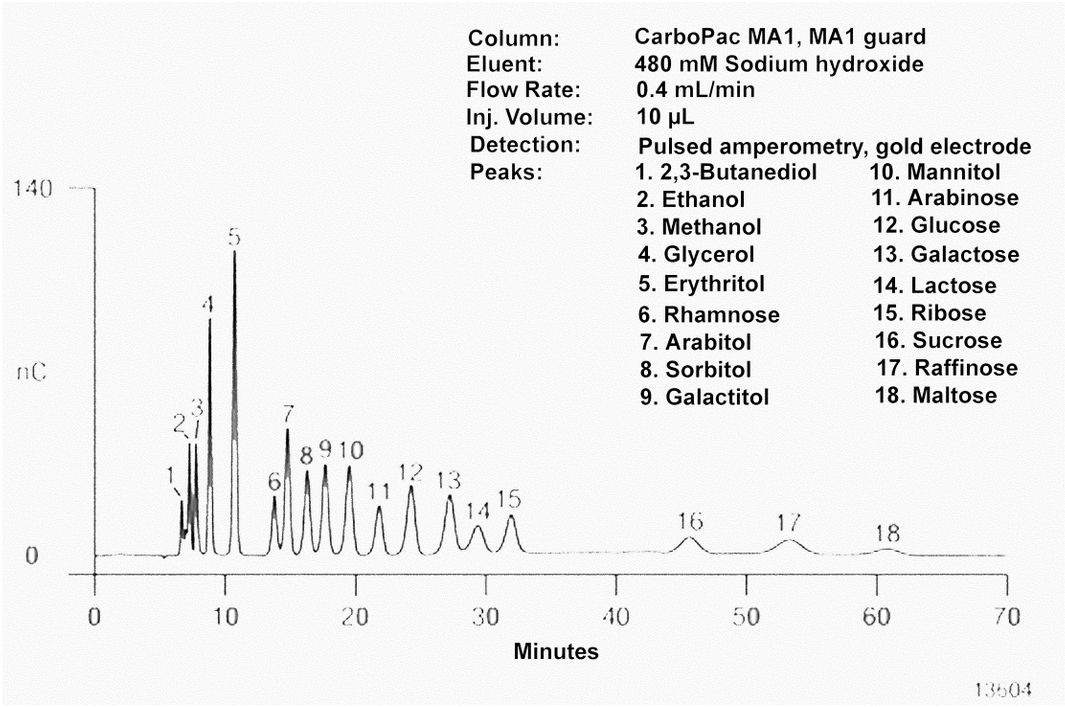

Fig. 3. Chromatogram demonstrating separation of carbohydrates, alditols, alcohols, and glycols on DIONEX CARBOPAC MA1 column followed by pulsed amperometric detection.

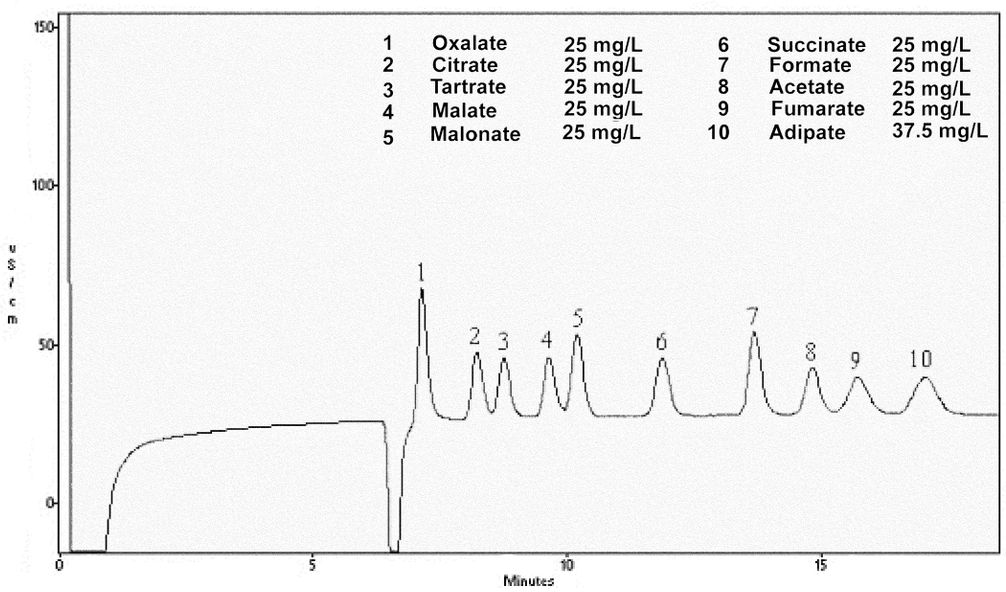

Fig. 4. Determination of organic acids by ion-exclusion separation followed by suppressed conductometric detection. Guard column (3.0 × 10 mm), analytical column (7.5 × 300 mm), eluent, 7.5 mM H_2SO_4 at the rate of 0.6 mL/min, MicroSuppressor (4.6 × 20 mm) regenerated with 0.6 M TMAOH, sample loop, 50 µL, conductometric detection.

Examples of the application of IC to pharmaceutical analysis are provided in *Tables 6–9*. Although these tables do not exhaustively capture the entire database of pharmaceutical applications of IC, they do provide relevant examples of the types of separation and detection strategies that are used in this field.

METHOD VALIDATION

Because IC is a liquid chromatographic method, guidelines for the validation of IC applications in the pharmaceutical industry are readily available (*70–72*), and most of the applications cited in this manuscript contain some degree of assay validation information. Comprehensive validation information, specifically with respect to the common validation parameters (e.g., accuracy, linearity, precision, specificity, sensitivity, and ruggedness), is summarized in *Table 10* for the various pharmaceutical applications of IC. Consistent with the nature of the application (trace analysis versus content/potency), the operating characteristics are similar to those that are routinely obtainable in more classical applications of liquid chromatography (e.g., HPLC).

Ion chromatography is extensively employed in the environmental and food industries. Because the requirements for quality in these disciplines are similar to those in the pharmaceutical industry, applications in these fields have been extensively validated, including the utilization of interlaboratory collaborative assessments (*61–68*).

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Table 1. Comparison of IC and HPLC

Item	IC	HPLC
1. Separation modes	Ion exchange, ion exclusion, and ion pair	Reversed phase, normal phase, size exclusion, affinity, and chiral
2. Band broadening	Typically follows Knox equation	Typically follows Knox equation
3. Mobile phase	Ionic mobile phases are commonly used. Solvents are sometimes added to enhance separation	Various solvents with or without buffers for pH adjustment
4. Suppressor for enhancing signal/noise ratio	Most commonly used for conductometric detection of anions and cations. Direct conductometric detection is suitable when detection at ppb levels is not necessary.	None
5. Detection	Conductivity, UV detection, postcolumn reaction followed by VIS detection, and pulsed amperometry	UV, diode-array, MS, RI, fluorescence, and postcolumn reaction followed by VIS detection
6. Instrumental setup	Resembles HPLC setup. Due to ionic mobile phases, system components preferably are made of inert materials.	Most of the system components are made of passivated 316 stainless steel, other metals, or plastic material.
7. Computer-based software	Very similar to that for HPLC	

Table 2. IC in USP monographs[1]

Title	Test	Separation	Detection[2]
Amikacin	Assay	Column: Anion Exchange, 8 µm, L47 packing, available as DIONEX's CarboPac MA1; Eluent: 0.115 N NaOH	PAD
Bethanecol chloride injection	Assay and limit of 2-hydroxypropyl trimethyl ammonium chloride	Column: Weak cation Exchange, 3–15 µm, L53 packing, available as DIONEX's CS14; Eluent: 20 mM methanesulfonic acid	NS, CD
Erythromycin ointment	Erythromycin assay	Column: Cation Exchange, 5–10 µm, L47 packing, available as TSK IC SW cation from TosoHaas; Eluent: mixture of ACN, NaOH, and water	PAD
Fludeoxyglucose F18 injection	Limit of 2-chloro-2-deoxy-D-glucose	Column: Anion Exchange, 10 µm, L46 packing; Eluent: 0.8% NaOH	PAD
Fenoldopam mesylate	Limit of iodide	Column: Anion Exchange, packing not specified; Eluent: 2.8 mM $NaHCO_3$ + 2.2 mM Na_2CO_3 + 0.8 mM 4-cyanophenol + 2% acetonitrile	S, CD
Ferumoxides Injection	Assay for citrate	Column: Anion Exchange, 15 µm, L48 packing, available as DIONEX's IonPac AS5; Eluent: 37.5 mM NaOH	S, CD
Kanamycin sulfate	Assay	Column: Anion Exchange, 8 µm, L47 packing, available as DIONEX's CarboPac MA1; Eluent: 0.115 N NaOH	PAD
Oil- and water-soluble vitamins with minerals oral solution	Assay for fluoride	Column: Ion Exclusion, 7–11 µm, L17 packing; Eluent: 10% (v/v) Ethanol + 2 mN H_2SO_4	CD
Oil- and water-soluble vitamins with minerals tablets	Assay for fluoride	Column: Ion Exclusion, 7–11 µm, L17 packing; Eluent: 10% (v/v) Ethanol + 2 mN H_2SO_4	CD
PEG 3350 and electrolyte oral solution	Assay of sodium and potassium	Column: Strong Cation Exchange, about 10 µm, L22 packing; Eluent: 1.9 mM HNO_3 eluent	NS, CD
	Assay of chloride and sulfate	Column: Weak Anion Exchange, about 10 µm, L23 packing; Eluent: Mixture of borate, gluconate, glycerine, and acetonitrile	NS, CD
Potassium Perchlorate	Assay of perchlorate	Column: Weak Anion Exchange, about 10 µm, L23 packing; Eluent: 10 mM phthalic acid + 10% methanol, pH 4.5	CD
Sodium fluoride F18 injection	Radiochemical purity (Purity of $N^{18}F$)	Column: Ion Exclusion, 7–11 µm, L17 packing; Eluent: 3 mN H_2SO_4	Gamma ray detector in series with CD
Streptomycin sulfate	Assay	Column: Anion Exchange, 15 µm, L48 packing, available as DIONEX's CarboPac PA1; Eluent: 70 mM NaOH	PAD

Table 2. IC in USP monographs[1] *(Continued)*

Title	Test	Separation	Detection[2]
Enoxaparin Sodium Injection (proposed)	Free sulfate content	Column: Strong Anion Exchange, 8 µm, L31 packing, available as DIONEX's IonPac AS11; Eluent: 3.0 mM Na_2CO_3	S, CD
Mg-carbonate, citric acid, and K-citrate for oral solution (proposed)	Assay for citrate	Column: Ion Exclusion, 7–11 µm, L17 packing; Eluent: 2 mM HNO_3	CD

[1] Information revised from reference 5.
[2] Detection: PAD, pulsed amperometric; NS, CD, nonsuppressed conductometric; CD, direct conductometric; S, CD, suppressed conductometric.

Table 3. Survey of stationary phases used in anion separations by ion chromatography[1]

Phase	Vendor	Functionality	Characteristics			
			Particle Size (µm)	Capacity (mequiv/g)	pH Range	Solvent Use (%)
A. Based on surface functionalized ethylenevinylbenzene/divinylbenzene copolymers						
PRP-X100	Hamilton	Aminated with triethylamine	10	0.2	1–13	100
PRP-X110	Hamilton	Quaternary ammonium	7	—[2]	0–14	100
LCA A01	Sykam	Quaternary ammonium	12	0.04	1–14	10
ExcelPak ICS-A23	Yokogawa	Quaternary ammonium	5	0.05	2–12	< 5
AN1	Transgenomic	Aminated with alyyl-diemthylethanolamine	10	0.05	2–12	< 5
AN300	Transgenomic	Aminated with alkyl-diemthylethanolamine	7	—[2]	2–12	< 5
Star Ion A300 IC	Phenomenex	Quaternary ammonium	—[2]	—[2]	1–12	< 5
B. Based on surface functionalized ethylvinylbenzene/divinylbenzene copolymers						
AS14[3]	Dionex	Quaternary ammonium	9	0.065[4]	2–11	100
AS14A[3]	Dionex	Quaternary ammonium	7[4]	0.12[4]	0–14	100
AS15	Dionex	Quaternary ammonium	9	0.225[4]	0–14	100
AS15A	Dionex	Quaternary ammonium	5	0.07[5]	0–14	100
C. Based on surface aminated polymethacrylate resins						
Shimpak IC-A1	Shimadzu	Quaternary ammonium	10	—[2]	2–11	10
Anion Dual 1[6]	Metrohm-Peak	Quaternary ammonium[7]	—[2]	—[2]	2–12	10
Anion Dual 2[6]	Metrohm-Peak	Quaternary ammonium	— [2]	— [2]	1–12	20
Polyspher IC AN-1	Merck	Quaternary ammonium	12	— [2]	2–10	20
Universal Anion	Alltech	Aminated triethylamine	10	0.1	2–12	5

Table 3. Survey of stationary phases used in anion separations by ion chromatography[1] *(Continued)*

Phase	Vendor	Functionality	Characteristics			
			Particle Size (μm)	Capacity (mequiv/g)	pH Range	Solvent Use (%)
MCI SCA04	Mitsubishi Kasei	Quaternary ammonium	5	0.03	2–12	5
D. Based on surface aminated polyvinyl resins						
ION-100	Interaction	Quaternary ammonium	10	0.1	0–14	10
Anion Supp 4[6]	Metrohm-Peak	Quaternary ammonium	9	0.046	3–12	100
Anion Supp 5[6]	Metrohm-Peak	Quaternary ammonium	5	0.094[4]	3–12	100
E. Silica-based anion exchangers						
Vydac 302 IC 4.6	Separations Group	Spherical particles with quaternary ammonium	10	0.1	2–8	100
Vydac 300 IC 405	Separations Group	Spherical particles with quaternary ammonium	15	0.1	2–10	100
269-001	Wescan (Alltech)	Spherical particles with quaternary ammonium	13	0.08	2–8	100
Nucosil 10 Anion	Macherey & Nagel	Spherical particles aminated with trimethylamine methyldiethylamine	10	0.06	2–8	100
TSK Gel IC-SW	Toya Soda	Spherical particles aminated with trimethylamine methyldiethylamine	5	0.4	2–8	100

Phase	Particle Diameter (μm)	Degree of Cross-linking (%)	Latex Particle Size (μm)	Capacity	Application
F. Based on latex-agglomerated anion exchangers (Dionex IonPac)					
AS4A-SC	13	0.5	160	30 μequiv/g	Universal
CarboPac PA1	10	5	350	100 μequiv per column	Sulfide/cyanide
AS7	10	5	350	—[2]	Polyvalent anions
AS9-SC	13	20	110	35 μequiv/g	Oxyhalides
AS9-HC	9	15	90	190 equiv per column[8]	High capacity, oxyhalides
AS10	8.5	5	65	170 μequiv per column[8]	Bromide, nitrate
AS11	13	6	85	45 μequiv/g	Gradients
AS11-HC	9	6	70	29 μequiv per column[8]	Gradients

Phase	Particle Diameter (μm)	Degree of Cross-linking (%)	Latex Particle Size (μm)	Capacity	Application
AS12A	9	0.2	140	60 μequiv/g	Fluoride, oxyhalides
AS16	9	1	200	170 μequiv per column[8]	Polarizable anions
AS17	10.5	6	75	30 μequiv/g	Gradients

Notes:
[1] From reference 6. This reference contains additional structural and technical properties of these phases and documents some typical separations.
[2] — = Not specified.
[3] IonPak.
[4] For a 250 × 4 mm column.
[5] For a 150 × 3 mm column.
[6] Metrosep.
[7] Based on hydroxyethylmethacrylate resin.
[8] Based on a 250 × 4 mm column.

Table 4. Survey of stationary phases used in cation separations by ion chromatography[1]

Phase	Vendor	Column Dimensions, mm	Characteristics			
			Particle Size (μm)	Capacity (mequiv/g)	pH Range	Solvent Use (%)
A. Based on surface-sulfonated styrene/divinylbenzene copolymers						
LCA-K01	Sykam	125 × 4	10	0.05	3	5
MCI Gel SCK01	Mitsubishi Kasei	150 × 4.6	10	—[2]	2	5
PRP-X200	Hamilton	250 × 4	10	0.035	8	100
Shimpack IC-C1	Shimadzu	150 × 4	10	—[2]	2	10
Cation/R	Alltech	100 × 3.2	10	0.04	2	40
TSK-Gel IC Cation	Toya Soda	50 × 4.6	10	0.012	2	10
B. Based on surface-functionalized ethylvinylbenzene/divinylbenzene copolymers						
CS12[3]	Dionex IonPac	250 × 4[6]	8.5	0.7[9]	—[2]	100
CS12A[4]	Dionex IonPac	250 × 4[7]	8.5	0.7[9]	—[2]	100
CS14[3]	Dionex IonPac	250 × 4[6]	8.5	0.325[9]	—[2]	100
CS15[5]	Dionex IonPac	250 × 4[6]	8.5	0.7[9]	—[2]	100
CS16[3]	Dionex IonPac	250 × 3[8]	5	3[10]	—[2]	100
C. Silica-based cation exchangers with sulfonic acid groups						
Vydac 400 IC 405	Separations Group	50 × 4.6	—[2]	0.5	—[2]	100
Nucleosil 5 SA	Macherey & Nagal	125 × 4	5	0.5	—[2]	100
TSK Gel IC Cation SW	Toyo Soda	50 × 4.6	5	0.5	—[2]	100
D. Silica-based cation exchangers with carboxylic acid groups						
Metrosep Cation 2[11]	Metrohm-Peak	250 × 4 150 × 4	7 7	0.194[12] 0.117[12]	5 5	100[13] 100[13]
LiChrosil IC CA (II)	E. Merck	100 × 4.6	5		—[2]	100
IC Pak cation M/D	Waters	150 × 3.9	5	1.5 ± 0.2	—[2]	100

Table 4. Survey of stationary phases used in cation separations by ion chromatography[1] *(Continued)*

Phase	Vendor	Column Dimensions, mm	Characteristics			
			Particle Size (μm)	Capacity (mequiv/g)	pH Range	Solvent Use (%)
Universal Cation[11]	Alltech	100 × 4.6	7	—[2]	—[2]	100
Universal Cation HR[11]	Alltech	100 × 4.6 53 × 7	3	—[2]	—[2]	100

Notes:
[1] Adopted from reference 6. This reference contains additional structural and technical properties of these phases and documents some typical separations.
[2] — = Not specified.
[3] Carboxylate groups.
[4] Carboxylate and phosphonate groups.
[5] Carboxylate, phosphonate, and crown ether groups.
[6] Also available in 250 × 2 mm size.
[7] Also available in 250 × 2, 150 × 3, and 100 × 2 mm sizes.
[8] Also available in 250 × 5 mm size.
[9] Mequiv/column based on a 250 × 4 mm column.
[10] Mequiv/column based on a 250 × 3 mm column.
[11] Poly(butadiene)-maleic acid–coated.
[12] Capacity per column.
[13] No methanol.

Table 5. Compatibility of conventional HPLC equipment for performing IC

Equipment	Composition of various components in the HPLC system that come in contact with the mobile phase	Recommended Solvents	Solvents to Avoid
Agilent 1100[1]	SST, gold, sapphire, ceramic, ruby, PTFE, FEP, PEEK, Quartz, Kapton, fused silica, vespel	- Various solvents. - Other details not available.	- Alkaline solutions with UV detection because they can attack quartz. - Alkali halides and their respective acids. - High concentration of inorganic acids, e.g., H_2SO_4 and HNO_3 at higher temperatures. - Halogenated solvents or mixtures that form radicals or acids. - Ether-containing peroxides: filter through Al_2O_3 to remove peroxides. - Solvents containing strong complexing agents, e.g., EDTA. - Mixtures of CCl_4 with 2-propanol or THF.
Waters 2695 Separations Module[2]	SST 316, zirconia ceramic, UHMWPE, sapphire, ruby, TEFZEL® (ETFE), TEFLON® (FEP and PTFE), TEFLON AF, FLUOROLY G, FLUORO-POLY-08R	- Various acids, e.g., methanesulfonic acid, 6 N HNO_3, and 0.2 M H_2SO_4, bases, e.g., NaOH, KOH, and 3 M NH_4OH, buffers, e.g., $NaHCO_3$, Na_2CO_3, and phosphate, and 100% solvents can be used.	- Perfluorosolvents: Attack or dissolve the TEFLON AF tubing in the degasser. - Halide salts: Avoid long-term exposure because they will cause pitting or corrosion of SS parts.
Waters 2795 Separations Module[3]	SST 316, UHMWPE, sapphire, ruby, Tefzel® (ETFE), TEFLON® (FEP and PTFE), PEEK, FLUOROLY G, FLUOROPOLY-08R	- Various acids, e.g., methanesulfonic acid, 6 N HNO_3, and 0.2 M H_2SO_4, bases, e.g., NaOH, KOH, and 3 M NH_4OH, buffers, e.g., $NaHCO_3$, Na_2CO_3, and phosphate, and 100% solvents can be used.	- Perfluorosolvents: Attack or dissolve the TEFLON AF tubing in the degasser. - Halide salts: Avoid long-term exposure because they will cause pitting or corrosion of SS parts.
Shimadzu, LC-2010 and VP series[4]	All the details not available	- Solvents. - Other details not available.	- Buffers or acids containing halogen (especially chloride) ions, because they cause pitting in the metal. - For PEEK in the flow path: Avoid THF, concentrated sulfuric acid, concentrated nitric acid, dichloromethane (also known as methylene chloride, MeCl, or DCM), dimethylsulfoxide (DMSO,) chloroform, or acetone because they will physically weaken the material.

Notes:
[1] From reference 74.
[2] From reference 75.
[3] From reference 76.
[4] From reference 77.

Table 6. Pharmaceutical applications of ion chromatography, active ingredients

Analyte	Column	Eluent	Detection	Other	Ref.
Disodium clodronate tetrahydrate	DIONEX IonPac AS7, 250 × 4 mm, 10 µm particles	40 mM HNO_3 at 0.5 mL/min	UV at 300 nm after post-column derivatization with acidic iron (III)	Stability-indicating versus degradation products with some validation data provided	12
1-(Butylamino)-1-deoxy-D-glucitol[1]	DIONEX IonPac CS3, 250 × 4 mm, 10 µm particles	10 mM HCl with 0.01 mM DL-2,3-diaminopropionic acid, 2 mL/min	Suppressed conductivity, 0.1 M TBAOH[2] regenerant	Stability-indicating versus common impurities with some validation data provided.	13
Alendronate[3]	WATERS IC-PAK HR (75 × 4.6 mm, 6 µm particles) or a Dionex OmniPac PAX-100 (250 × 4 mm, 8 µm particles)	1.6 mM HNO_3 or 1.76 mM HNO_3 with 20% acetonitrile at 0.5 mL/min	Direct conductivity	Analysis in intravenous solution, validation data provided	14
Aredia[4]	ALLTECH Universal Anion	5 mM potassium nitrate, pH 3.5, 1.2 mL/min	Refractive index	Quantitation in dosage forms, stability-indicating versus formulation components, impurities and degradation products	15
Alendronate sodium,[3] etidronate disodium,[5] clodronate disodium[6]	WATERS IC-PAK HR anion (75 × 4.6 mm, 6 µm particles) and others[7]	Nitric acid or nitric acid–potassium nitrate mixtures, 0.5–1.0 mL/min	Indirect UV at 235–245 nm	Validation of method for drug analysis in tablets and i.v. formulations	16
Alprenolol,[8] atenolol,[9] acebutolol,[10] metopropolol,[11] oxprenolol,[12] propranolol[13]	WATERS IC-PAK CM/D (5 µm particles)	50 mM HNO_3 in 4% acetonitrile, 1 mL/min	UV at 270 nm	Validation of method for drug analysis in tablets and i.v. formulations	17
Alendronate, clodronate, etidronate	HAMILTON PRP-X100, 250 × 4.1 mm, 10 µm particles	1 mM trimesic acid, pH 5.5 at 1 mL/min	Indirect UV at 254 nm	Stability-indicating versus thermal degradation products, influence of mobile phase composition explored	18
Sodium salicylate, ampicillin sodium, potassium guaiacolsulfonate, benzylpencillin potassium	BIO TECH RESEARCH Carbon B1-01, 100 × 4.6 mm	0.1 M Pyrocatechol Violet–2 mM HNO_3 at 0.8 mL/min	Suppressed conductivity with TBAOH as regenerant	Indirect drug quantitation via the counterions (Na, K). Some validation data provided.	19
Caffeine, theobromine, theophylline[14]	DIONEX HPIC-CS3 (cation, 2 columns in series) DIONEX OMNIPAC PAX-100 (anion)	100 mM HCl at 1 mL/min (cation) 15 mM KOH in 1% acetonitrile at 1 mL/min (anion)	Direct UV at 274 nm	Quantitation in injections and tablets, some method optimization and validation data provided.	20
Paracetamol[15]	WATERS IC-PAK A HR (10 cm, 6 µm particles)	5 mM LiOH in 5% acetonitrile at 1 mL/min	Direct UV at 300 nm	Quantitation in solid dosage forms.	21
Oxytetracycline, tetracycline, chlortetracycline, doxycycline	DIONEX OMNIPAC PCX-100 (250 × 4 mm)	0.2 M HCl in ≈ 28% acetonitrile at 1 mL/min	Direct UV at 300 nm	Method developed primarily for residuals testing	22

Table 6. Pharmaceutical applications of ion chromatography, active ingredients *(Continued)*

Analyte	Column	Eluent	Detection	Other	Ref.
Benzethonium chloride, cetylpyridium chloride, chlorhexidine digluconate, cetrimonium bromide, domiphen bromide	SHIM-PACK IC-A1 (100 × 4.6 mm, 10 µm)	0.94 mM sodium carbonate + 0.31 mM sodium bicarbonate or 0.25 mM phthalic acid + 2.4 mM tris(hydroxymethyl)aminoethane, pH 4.31, both at 1.5 mL/min	Direct conductivity	Sample combusted and analyzed via the liberated anion (Cl or Br). Analytical recoveries reported.	23
Copper, manganese, zinc	DIONEX HPICE-CS5	0.05 M oxalic acid (pH 5.24) at 1 mL/min	UV-VIS at 520 nm after postcolumn reaction with PAR	Used to characterize multivitamin supplements.	69
Chloride, bromide	DIONEX IONPAC AS4A	0.75 mmol/dm^3 sodium bicarbonate, 2.2 mmol/dm^3 sodium carbonate at 1 mL/min	Suppressed conductivity with 25 mmol/dm^3 sulfuric acid as regenerant	Used to assess batch-to-batch variation in an ion-exchange bile acid sequestrant	60

Notes:
[1] A polyhydroxy aliphatic amine synthetic reaction intermediate.
[2] TBAOH = tetrabutylammonium hydroxide.
[3] Monosodium monohydrate salt of 4-amino-1-hydroxybutane-1,1-bis-phosphonic acid.
[4] Disodium-3-amino-1-hydroxy-propylidene-1,1-biphosphonate pentahydrate.
[5] 1-Hydroxyethane-1,1-bisphosphonic acid disodium salt.
[6] 1,1-Dichloromethane-1,1-bisphosphonic acid, disodium tetrahydrate salt.
[7] Other columns include DIONEX AS7 and AS4A and METACHEM HEMA 1000Q.
[8] 1-(*o*-Allylphenoxy)-3-isopropylamino-2-propanol.
[9] 1,4-(2′-Hydroxy-3′-isopropylamino-propoxy)phenylacetamide.
[10] N-3-Acetyl-4-(2-hydroxy-3-(isopropylamino)-propoxy)-phenylbutanamide.
[11] 1-Isopropylamiono-3-(*p*-(β-methyloxyethyl)phenoxy)-2-propanol.
[12] 1-(2-(Allyloxy)-phenoxy)-3-isopropylamino-2-propanol.
[13] 1-Isopropylamino-3-(1-napththyoxy)-2-propanol.
[14] Separations as anions and cations reported.
[15] Acetominophen, N-acetyl-*p*-aminophenol.

Table 7. Pharmaceutical applications of ion chromatography, excipients and inactive formulation components

Analyte	Column	Eluent	Detection	Other	Ref.
Acetate, lactate, chloride, phosphate citrate, sulfate	HAMILTON PRPX-100, 250 × 4.1 mm; WATERS IC PAK A, 50 × 4.6 mm, VYDAC 300 IC, 50 × 4.1 mm	Various potassium hydrogen phthalate solutions (some with acetonitrile at 1.3–2.0 mL/min	Indirect UV at 254 nm	Used to measure these anions in i.v. solutions	24
Oxalate	DIONEX AS-1	1 mM potassium hydrogen phthalate, 2 mM sodium borate, pH 9.1 at 2–4 mL/min	Indirect UV at 250 nm	Recovery data provided from a generalized pharmaceutical LVP solution.	25
Lactic acid and lactic acid lactate	DIONEX HPICE-AS1 (ion exclusion)	1 mM sodium octanesulfonate	Suppressed conductivity	Used to characterize Amrinone Lactate Injection	26
Sodium, potassium, cesium, magnesium, calcium	ZORBAX SCX-300, 250 × 4.6 mm	2.5 mM copper sulfate at 1.2 mL/min	Indirect UV at 230 nm	Used for the analysis of a cardioplegic solution, some validation data	27
Sodium lauryl sulfate	DIONEX OMNIPAC PAX-500, 250 × 4 mm	Gradient used[1] at 1 mL/min	Suppressed conductivity, 12.5 mM sulfuric acid as regenerant	Characterization of tablet dosage form	28
Chloride, sulfate, phosphate, citrate	DIONEX OMNIPAC PAX-500, 250 × 4 mm	40 mM NaOH in 5% methanol at 1 mL/min	Suppressed conductivity, 12.5 mM sulfuric acid as regenerant	Characterization of a liquid veterinary drug	28
Citrate	HAMILTON PRP-X100, 150 × 4.1 mm, 10 µm particles	0.875 mM trimesic acid, pH 10.0 at 1.5 mL/min	Indirect UV at 280 nm	Used to characterize a number of commercial pharmaceutical products, validation data provided	29
Methane through octane sulfonic acids	DIONEX PAX-500	Gradient used[2] at 1 mL/min	Suppressed conductivity with 12.5 mM sulfuric acid regenerant	Validation data provided	30
Methanesulfonic acid, fumaric, maleic, succinic, tartaric acids	DUPONT ZORBAX NH_2, 250 × 4.6 mm, 5 µM particles	20 mM sodium dihydrogen phosphate, 0.13 mM phosphoric acid (pH 4.2) in 5% acetonitrile	Direct conductivity	Method development data provided.	31
Chloride, bromide, sulfate	BIO TECH RESEARCH Carbon BI-01, 100 × 4.6 mm	2 mM sodium carbonate, 1 mM tetrabutylammonium-hydroxide, 5% acetonitrile at 0.8 mL/min	Suppressed conductivity, 12.5 mM sulfuric acid regenerant	In D&C color additives. Sample analysis by direct injection or after oxygen flask combustion.	32
Oxalate, citrate	DIONEX AS-1	10 mM TRIS, 30 mM sulfate, pH 6.5 at 1 mL/min	Direct UV at 210–220 nm	Accuracy documented in a number of i.v. products.	33
Acetic, malic, lactic acids	BIO-RAD Aminex HPX-87H, 300 × 7.8 mm	0.15% sulfuric acid or 0.005% phosphoric acid at 0.8 mL/min	Direct UV at 210 nm	Ion exclusion method. Assay validation data provided for use in TPN solutions.	34
Malic, citric, and tartaric acids	SHIMPACK IC-A1, 100 × 4.6 mm, 12.5 µm particles	1.5 mM phthalic acid at pH 4.0 at 1.2 mL/min	Series bulk acoustic wave detector	Reported to be 5X more sensitive than direct conductivity. Used to characterize a homeopathic drug.	35

Table 7. Pharmaceutical applications of ion chromatography, excipients and inactive formulation components *(Continued)*

Analyte	Column	Eluent	Detection	Other	Ref.
Phosphate, phosphite, hydrophosphite	WATERS IC-PAK A HR, 6 µm particles	Gluconate/borate buffer containing acetonitrile and *n*-butanol at 1 mL/min	Direct conductivity	Used to characterize several tablet and syrup products.	36
Sulfite	WESCAN Anion Exclusion H/S, 250 × 4.6 mm	20 mM sulfuric acid at 0.75 mL/min	Direct conductivity	Used to characterize several herbal medicines.	37
Additives in foods and pharmaceutical preparations[3]	SHIMADZU SHIM-PACK IC-A3, 150 × 4.6 mm, 5-µm particles	5 mM sodium phosphate monobasic (pH 8.2) with 4% acetonitrile at 1 mL/min	Direct UV, switched between 205 and 227 nm	Some assay validation and performance data provided (tablet dosage form).	38
Acetic and lactic acids	ALLTECH Anion Exclusion, 300 × 7.8 mm	2 mM sulfuric acid at 0.7 mL/min	Direct conductivity	Validation of an ion-exclusion method for use in characterizing LVP products.	39
Silicic acid, calcium, magnesium, aluminum	TOSOH TSK gel IC-Anion-PW (50 × 4.6 mm, 10-µm particles)	1 mM NaOH with 10% methanol at 1.2 mL/min	Conductivity	Cations separated as their EDTA complexes. Validation data provided.	40

Notes:
[1] This separation utilized a 60-minute gradient formed with four eluents including water, acetonitrile/water (90/10), 200 mM NaOH, and methanol/water (45/55).
[2] A = 5 mM sodium borate, 5% acetonitrile; B = 20 mM sodium borate, 40% acetonitrile. Time = 0 min, 100% A. Time = 10 min, 100% B. Time = 15 min, 100% B.
[3] Analytes included saccharin, aspartame, acesulfame-K, benzoic acid, sorbic acid, caffeine, theobromine, and theophylline.

Table 8. Pharmaceutical applications of ion chromatography, degradation products and impurities

Analyte	Column	Eluent	Detection	Other	Ref.
5-hydroxymethylfurfural (5-HMF)	WESCAN Anion Exclusion HS, 100 × 4.6 mm	10 mM sulfuric acid at 0.8 mL/min	UV detection at 285 nm	Performance contrasted favorably with reversed-phase HPLC method.	41
Aluminum	WATERS Protein-Pak SP-5PW, 75 × 7.5 mm	0.01 M potassium sulfate, pH 3.0 at 1 mL/min	Fluorescence (395 nm excitation, 500 nm emission) with postcolumn reaction	Used for the quantitation of trace levels of Al in pharmaceutical diluents.	42
Cyanamide[1]	DIONEX ION-PAC AS-10	50 mM NaOH in 1% acetonitrile	PAD	Validation information provided.	43
Common anions[2]	DIONEX IONPAC AS4A	1.75 mM sodium bicarbonate, 2.5 mM sodium carbonate at 1 mL/min	Suppressed conductivity	Characterization of high-purity water for sub-ppb trace ionic contaminants with preconcentration.	44
Common cations[3]	DIONEX IONPAC CS12	20 mM methanesulfonic acid at 1 mL/min	Suppressed conductivity	Characterization of high-purity water for sub-ppb trace ionic contaminants with preconcentration.	44
Sulfamate, sulphate	HAMILTON PRP-X100 (150 × 4.6 mm, 10-µm particles)	5.8 mM *p*-hydroxybenzoic acid, 2.5% methanol at pH 9.4, 1.5 mL/min	Indirect UV at 310 nm	Degradation products of Topiramate.	45
Methansulfonic acid	HAMILTON PRP-X100 (150 × 4.1 mm, 10-µm particles)	Acetonitrile/60 mM NaOH (20/80) at 2 mL/min	Suppressed conductivity with 50 mN sulfuric acid as regenerant.	Measured this drug synthesis intermediate in drug raw materials; some validation data provided.	46
Citric, malic, ascorbic acid	SHIM-PACK IC-A1 (100 × 4.6 mm)	20 mM potassium hydrogen phthalate at 1 mL/min	Direct conductivity and quartz crystal detector	Used to determine these components in a Chinese herbal medicine.	47
Amylamine, *tert*-butylamine	DIONEX CS-14 (250 × 4 mm, 5-µm particles)	Acetonitrile/50 mM methanesulfonic acid (5/95) at 1 mL/min	Suppressed conductivity with 100 mM tetrabutyl ammonium hydroxide as regenerant.	Amylamine is a synthetic residual and *t*-butylamine is the active's counterion (measured for purity assessment).	48
Nitrite, nitrate	EXSIL SAX (125 × 4.6 mm)	22 mmol/dL potassium dihydrogen phosphate, 3 mmole/dL phosphoric acid with 20% acetonitrile at 1.6 mL/min	Direct UV at 214 nm, or electrochemical	Used to study the oxidative denitrification of hydroxyguanidines.	49
Carbonate	DIONEX IONPAC ACE-AS1 (ion exclusion)	Water at 1 mL/min	Conductivity	Used to study the oxidative decarboxylation of aromatic carboxylic acids	49
Sulfate	DIONEX AS4-SC	1.8 mmol/dL sodium carbonate, 1.7 mmol/dL sodium bicarbonate at 1.5 mL/min	Direct UV at 214 nm or suppressed conductivity	Used to study the generation of sulfate from perthiol drugs.	49

Table 8. Pharmaceutical applications of ion chromatography, degradation products and impurities *(Continued)*

Analyte	Column	Eluent	Detection	Other	Ref.
Methanesulfonic acid	DIONEX IONPAC AS4A-SC	0.015% sodium hydrogen carbonate at 2 mL/min	Suppressed conductivity with 0.075% sulfuric acid as regenerant	Hydrolysis of busulfan tablets; validation data provided.	50
Oxalic acid, oxamic acid, and oxamide	DIONEX IONPAC ICE-AS1 (250 × 9 mm, 7.5-µm particles)	5/95 acetonitrile/0.1% sulfuric acid at 0.8 mL/min	UV at 205 nm	Impurity products in synthetic processes; some validation data provided.	51
Sulfate and sulfamate	DIONEX IONPAC AS5A-5µ (150 × 4 mm)	Gradient with mobile phase A being water and mobile phase B being 50 mM NaOH at 1 mL/min	Suppressed conductivity	Assay used to measure these analytes as degradation products of Topiramate. Extensive validation information provided.	59

Notes:
[1] Synthetic residue.
[2] Including chloride, nitrite, bromide, nitrate, orthophosphate, and sulfate.
[3] Including lithium, sodium, ammonium, potassium, magnesium, and calcium.

Table 9. Pharmaceutical applications of ion chromatography, process streams

Analyte	Column	Eluent	Detection	Other	Ref.
Carbohydrates (galactose, glucose, ribose, fructose)	DIONEX CARBOPAC PA1 (250 × 4 mm)	150 mM NaOH at 1 mL/min[1]	PAD (Au electrode)	Methods used to quantitate substrates and metabolites in fermentation broth	52
Inorganic cations (calcium, magnesium, ammonium, potassium, sodium)	DIONEX IONPAC CS10 (250 × 4 mm)	20 mM HCl, 4 mM *d,l*-2,3-diaminopropionic acid at 1 mL/min	Suppressed conductivity with 0.1 M tetrabutylammonium hydroxide as regenerant		
Sugar alcohols (glycerol, inositol, mannitol, sorbitol)	DIONEX HPICE-AS1 (250 × 4 mm, ion exclusion	100 mM perchloric acid at 0.8 mL/min	PAD (Pt electrode)		
Sodium, ammonium, potassium, magnesium, calcium	DIONEX IONPAC CS12 (250 × 4 mm)	4 mM methanesulfonic acid at 1 mL/min	Suppressed conductivity	Used to optimize culture media composition.	53
Chloride, nitrate, sulfate	Ion exclusion: BIORAD Organic Acids column HPAH (100 × 7.8 mm, 9-µm particles) Ion exchange: Dionex AS4A	Ion Exclusion: 1 mM octanesulfonic acid with 2% isopropyl alcohol Ion Exchange: 2.8 mM sodium carbonate, 1.7 mM sodium bicarbonate, both at 2 mL/min	Suppressed conductivity with suppression for both the ICE and IC separations	Coupled ion exclusion (online sample preparation) with ion exchange (analytical separation) to analyze these analytes in fermentation broth containing high levels of organic acids.	54
Dimethylbenzenesulfonate	DIONEX OMNIPACK PAX-100	5 mM sodium chloride, 0.2 mM sodium hydroxide, 32% acetonitrile at 1 mL/min	Direct UV at 220 nm	Used to perform residuals testing during cleaning validation.	55
Magnesium	SHIM-PACK IC-C1 (150 × 5 mm, 10-µm particles)	4 mM tartaric acid, 2 mM ethylenediamine at 1.5 mL/min	Double cell bulk acoustic wave detector	Used to follow decrease in magnesium levels in cell culture media.	56
Hydroxylamine	DIONEX CS14 (250 × 4 mm)	11 mM sulfuric acid at 1 mL/min	PAD, Au working electrode	Analyte is a mutagenic active ingredient raw material, levels of which were monitored in final waste streams before disposal.	57
Chloride, nitrate, sulfate	DIONEX AS4A-SC	1.8 mM sodium carbonate, 1.7 mM sodium bicarbonate at 2 mL/min	Suppressed conductivity	Validated as the EP method for characterizing Purified Water.	58
Ammonium, magnesium, calcium	DIONEX CS 12	20 mM methanesulfonic acid at 1 mL/min	Suppressed conductivity	Validated as the EP method for characterizing Purified Water.	58

Note:
[1] A gradient separation for the carbohydrates is also reported.

Table 10. Examples of validation data for quantitative ion chromatography methods

Application	Performance Parameters						Ref.
	Accuracy	Precision	Linearity	Specificity	LOQ/LOD	Ruggedness	
A. Active ingredient analysis							
Alendronate in i.v. and tablet formulation by suppressed conductivity detection	Spiked drug into placebo at 80, 90, 100, 110, and 120% of formulation level. Mean recovery, 100.2%. Demonstrated equivalence versus an HPLC/fluorescence method.	Injection, $n = 10$ at 0.05 mg/mL, 1% RSD by peak height. Total method, $n = 10$ at 2.5 mg/mL 1.1% RSD or less.	Coefficients of determinations of 0.999 or greater for range of 40–160% of assay level. Non-zero intercepts observed.	Tested against formulation placebo and known thermal decomposition products.	Not evaluated.	Evaluated by performing testing on four analytical systems.	14
Biphosphonate drugs with indirect UV detection	Spiked drug into placebo at 50, 75, 100, 125, and 150% of formulation level. Mean recovery for three drugs, 100± 1% at sample level of 0.05 mg/mL.	Injection to injection, $n = 10$ at 0.05 mg/mL (25 µL injection) or 0.4 mg/mL (50 µL injection). %RSD less than 1%. Total method, 1–2% RSD for $n = 10$.	Coefficients of determinations of 0.999 or greater for range of 20–200% of formulation level. Areas better than heights; non-zero intercepts observed.	Tested against formulation placebo and known thermal decomposition products.	LOD of 0.001 mg/mL at S/N of 4 for all analytes	Evaluated via two analysts/two system testing, testing using five columns, and examining performance on one column after at least 500 injections.	16
Disodium clodronate in bulk materials pharmaceuticals by UV with postcolumn derivatization	Spiked drug into placebo capsules and tablets at 80, 100, and 120% of nominal formulation level (300–1000 mg). Mean recovery = 99.5–100.7%.	Six samples of bulk material and pharmaceuticals assayed. %RSD from 0.8% to 1.3% for 60–820 mg of drug.	50–175% of nominal analyte conc. (0.02–0.07 mg/mL), $r^2 = 0.9999$ ($n = 6$ at each level).	Tested against formulations degraded by acid, base, peroxide, heat, UV light) and against mixture of known impurities.	Not evaluated.	Stability of sample solutions = 60 hours at RT. Tested two columns with system suitability tests.	12
SPE removal of nonpolar compounds, ion-exclusion separation, and UV detection of citrate and acetate in medical fluids	Recovery, compared with non-SPE treated, ranged from 99.9 to 100.3% for 80 to 120% concentration.	%RSD ranging from 0.0 to 0.3%.	r^2 0.999, with % y-intercept ≤0.6.	The SPE treatment did not introduce citrate or acetate.	Not evaluated.	Two analysts on separate systems. Pooled data, 99.9 to 100.2% recovery, and %RSD ≤0.3.	73
B. Excipients and inactive ingredients							
Methane sulfonic acid in intermediates and drug substances by direct conductivity	Determined by mass-balance calculations in batch-release applications.	Injection precision, 1–2% RSD. Method precision, 1–3% RSD.	$r^2 = 0.9997$ over the range of 0.1–5 mg/mL.	Extensive investigation of elution characteristics.	Not evaluated.	Not evaluated.	31

Table 10. Examples of validation data for quantitative ion chromatography methods *(Continued)*

Application	Performance Parameters						Ref.
	Accuracy	Precision	Linearity	Specificity	LOQ/ LOD	Ruggedness	
Alkyl sulfonic acids (for example, methansulfonic acid, MSA) by suppressed conductivity, total method performance (sample extraction)	Spiked samples at 6 levels between 80 and 120% of allowable limit, mean recovery (n = 6) = 102.9%.	Injection precision (n = 5) at the specification limit was 5% RSD.	r^2 = 0.9999 over application range.	Resolution demonstrated versus other sulfonic acids and chloride.	LOQ of 40 ppm (µg/g) in sample for MSA.	Stock solutions of analytes stable for 1 week at RT. Analyzed 4 samples across 2 days, two columns, and fresh mobile phase preparations. %RSD = 7.5%.	30
Acetic and lactic acids in LVP i.v. solutions by ion exclusion with direct conductivity	Autoclaved formulation blanks spiked with 80, 100, or 120% of product specification levels. Acetate recovery 99–101%, 1500–7900 mg/L. Lactate, 99–103%, 680–3800 mg/L.	For 5 preparations in 4 formulations, 0.35–1.2% RSD at levels from 840 to 6600 mg/L.	Examined at 50 to 150% of sample dilution target with 5 standards, triplicate injections each (150–450 mg/L for sodium acetate trihydrate, 50 to 150 mg/L for sodium lactate). r^2 = 0.9997; other data provided.	Autoclaved formulation blanks examined. Examined a test sample cocktail containing 13 dextrose impurities, related substances, ''foreign sugars,'' and decomposition products.	LOQ = 9.9 mg/L for sodium acetate trihydrate and 3.6 mg/L for sodium lactate.	Performed accuracy assessment with two runs (different analysts and columns). No difference in performance noted. Also examined robustness and response stability.	39
C. Impurities and/or degradation products							
Cyanamide as a synthesis residual via PAD	Bulk drug substance spiked with 3 to 25 ppm additional analyte, % recovery from 89 to 106%.	Ten injections of sample at 5.4 ppm, %RSD = 4.6%. Method precision tested with 8 preparations of one lot, %RSD = 6.4%.	Assessed over the range of 15–150 ng/mL (7 levels, duplicate injections per level), r^2 = 0.9982.	Absence of response noted in degraded bulk drug substance.	Minimum quantifiable limit = 3 ppm.	Sample solutions stable for 53 hours at RT.	43
Methanesulfonic acid as a synthesis impurity with suppressed conductivity	Batch of drug spiked with MSA levels of 0.1–2.0% (by weight), duplicate injections at 7 levels, % recovery 98–107%.	Six preparations of bulk drug, %RSD = 0.51%. Day-to-day reproducibility of 2.9–4.0% RSD.	Assessed over a range of 1–20 ppm, r^2 > 0.999 (n = 10)	Absence of response noted in formulation placebos.	LOD = 0.3 ppm.	Assessed as day-to-day reproducibility.	46
Oxalic acid, oxamic acid, and oxamide as synthetic impurities by ion exclusion with UV detection	Examined by comparing calibration curves obtained in water matrix versus API. Less than 5% difference in slope, water versus API.	For six replicate preparations, %RSD = 9.3% at 2 ppm for oxalic acid; 4.1% at 1 ppm for oxamic acid; and 3.4% at 0.6 ppm for oxamide.	r^2 = 0.9999 over range of 0.4–24 ppm for oxalic and oxalic acids; 0.1 to 6.2 ppm for oxamide. Six concentrations, replicate injections.	Blank API matrix repetitively injected with no interfering peaks.	LOQ of 0.2 to 0.6 ppm.	Standards and samples stable for 24 hours at RT. Method tested in two different laboratories with new and aged columns.	51

Table 10. Examples of validation data for quantitative ion chromatography methods *(Continued)*

Application	Performance Parameters						Ref.
	Accuracy	Precision	Linearity	Specificity	LOQ/ LOD	Ruggedness	
Sulfate and sulfamate, decomposition products of topiramate, by suppressed conductivity	Examined by analyzing tablets spiked with the analytes over the range of 0.24–1.0 mol%. Mean recovery of 103%.	1.1% RSD (10 injections) for sulfamate and 1.5% RSD for sulfate at 0.5 mol%.	0.04 to 27 mol% for sulfamate, 0.1 to 30 mol% for sulfate, $r^2 > 0.999$ but systematic skew in calibration curve noted.	Formulation placebo (degraded and fresh) examined for absence of interfering peaks.	LOQ = 0.05 mol% for sulfamide, 0.1 mol% for sulfate.	Samples and standards stable for at least 6 days at RT. Performed robustness assessment.	59
D. Process streams							
Inorganic cations in culture media by suppressed conductivity	Spike recoveries determined in chemically defined and complex media formulations.	Interday ($n = 6$) and intraday ($n = 12$) precision assessed at concentrations ranging from 0.5 to 50 ppm. At > 1 ppm, interday %RSD < 1%, intraday < 2%.	$r^2 > 0.9999$ using polynomial model, 0.5 to 25 ppm for Na and K, 1 to 50 ppm for ammonium, Ca, Mg.	Specificity considered from a theoretical perspective based on the separation and detection methods.	LOD 0.5 to 1 ppm.	Assessed via intraday precision.	53
Hydroxylamine in waste streams by PAD	Mean recoveries of analyte spiked into waste water of 69.4% at 0.05 ppm and 93.3% at 0.5 ppm.	Triplicate injections at 0.05 ppm and 0.5 ppm had %RSD of 2.8% and 1.5%.	$r^2 = 0.999$ over range of 0.01 to 2.0 ppm.	Examined versus a mixture of *n*-methylhydroxyamine analogs at 1 ppm.	LOQ = 0.015 ppm.	Standards stable for 12 hours at RT.	57

Table 10. Examples of validation data for quantitative ion chromatography methods *(Continued)*

Application	Performance Parameters						Ref.
	Accuracy	Precision	Linearity	Specificity	LOQ/ LOD	Ruggedness	
Chloride, nitrate, sulfate in pharmacopeial grades of water with suppressed conductivity	Recovery in solutions at 75%, 100%, and 125% of nominal standard concentration. Mean accuracy = 105.1% for Cl; 104.5% for nitrate; 105.3% for sulfate.	Method repeatability assessed by six injections on one day at the specification limit. %RSD = 5.0% for Cl, 3.3% for nitrate, 0.7% for sulfate. Method reproducibility assessed by duplicate injections on six different days by different analysts. %RSD for Cl = 12.4%, 7.8% for nitrate, 4.0% for sulfate.	Duplicate injections for 5 standards over range of 25–150% of the pharmacopeial limit (0.1 ppm Cl, 0.2 ppm nitrate, 1 ppm sulfate); $r^2 >$ 0.99.	Tested against other common inorganic anions.	LOQ = 0.05 ppm, Cl; 0.004 ppm, nitrate; 0.04 ppm sulfate.	Standards and samples stable for > 7 days at RT. See method reproducibility.	58
Ammonium, magnesium, calcium in pharmacopeial grades of water with suppressed conductivity	Recovery in solutions at 75%, 100%, and 125% of nominal standard concentration. Mean accuracy = 97.9%% for ammonium; 98.5% for magnesium; 98.4% for sulfate.	Method repeatability assessed by six injections on one day at the specification limit. %RSD = 2.7% for ammonium, 1.7% for magnesium, 0.4% for calcium. Method reproducibility assessed by duplicate injections on six different days by different analysts. %RSD for ammonium = 5.4%, 1.7% for magnesium, 2.6% for calcium.	Duplicate injections for 5 standards over range of 25–150% of the pharmacopeial limit (0.2 ppm ammonium, 1.0 ppm magnesium, 2 ppm calcium); $r^2 >$ 0.99.	Tested against other common inorganic cations.	LOQ = 0.02 ppm, ammonium; 0.25 ppm, magnesium; 0.35 ppm calcium.	Standards and samples stable for > 7 days at RT. See method reproducibility.	58

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The Role of Rapid Microbiological Methods within the Process Analytical Technology Initiative

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ABSTRACT This article discusses the role of rapid microbiological methods for in-process and finished-product testing within the context of the FDA Process Analytical Technology Initiative. The disadvantage of the extended incubation time required by growth-based microbiological methods is emphasized in this stimuli article. The authors briefly review candidate technologies for rapid microbiological testing. Using risk assessment tools, the authors identify critical microbial tests where these rapid microbiological methods could be applied.

In November 2001 Janet Woodcock, MD, Director, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration, outlined the agency's Process Analytical Technology (PAT) Initiative to promote innovation in manufacturing process research and development to achieve drug quality improvements in the U.S. pharmaceutical industry (*1*). The PAT subcommittee of the Advisory Committee for Pharmaceutical Science was established and chaired by Ajaz Hussein, PhD, Deputy Director, CDER, Office of Pharmaceutical Sciences. This initiative is designed to address manufacturing-related quality problems within the industry by encouraging process innovation in a regulatory risk-adverse industry.

PAT has been defined as systems for analysis and control of manufacturing processes based on timely measurements during processing, and control of critical quality parameters and performance attributes of raw and in-process materials and processes to ensure acceptable end-product quality at the completion of the process.

At the 23 October 2002 PAT subcommittee meeting presentations (*2*) were made on the PDA Technical Report No. 33, The Evaluation, Validation, and Implementation of New Microbiological Testing Methods (Jeanne Moldenhauer (Vetech Pharmaceutical Consultants, Inc.) and the role of rapid microbiological methods in PAT (Dr. Robert Johnson and colleagues, GlaxoSmithKline). Also there was an afternoon breakout session moderated by Dr. Peter Cooney to discuss the role of Rapid Microbiological Methods (RMM) within the PAT Initiative. Drs. Michael Korcynzski and Scott Sutton, members of the USP Analytical Microbiology Expert Committee, participated in the breakout session. When Dr. Korcynzki summarized feedback from the breakout sessions, he emphasized that the overriding concerns were the acceptance of rapid methods by regulatory agencies and the complexity of the validation of new microbiological testing methods.

In the pharmaceutical and biotechnology industries, microbial testing may be divided into two areas: first, in-process monitoring and second, product release testing. Examples of in-process monitoring are incoming pharmaceutical ingredient testing, water for pharmaceutical purposes monitoring, intermediate monitoring, and microbial monitoring of personnel and the manufacturing environment. Product release testing includes microbial limit testing of nonsterile drug products, sterility testing of finished product, microbial assay of vitamins and antibiotics, and microbial identification. Typically, because of the extended testing cycle time for classical microbial tests, the results of both the in-process monitoring and product release testing are reviewed as part of the product release and do not immediately influence the manufacturing process.

Classical microbial tests require extended cycle times because they rely on the growth of microorganisms on microbiological culture media. Classical microbial detection is based on the development of turbidity or other indicators of microbial growth in liquid media and of colonies on solid media. The cultivation of microorganisms includes a pregrowth phase that includes the germination of bacterial and fungal spores and the resuscitation of stressed vegetative bacterial and fungal cells, a lag phase for the biochemical and physiological acclimatization of the cells to the media, and a logarithmic phase during which the cells are actively dividing. Rapidly growing bacterial cells may have a generation time of the order of 20 minutes, and most microorganisms isolated from pharmaceutical ingredients, intermediates, and products are stressed. Thus, the lag phase may be extended, and the time for microbial detection and/or enumeration typically ranges from 2 to14 days of incubation. *Table 1* summarizes the classical microbial tests and their incubation times.

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Table 1. Examples of in-process microbial monitoring and product release tests and their incubation times

Type of Microbial Test	Microbial Test	Incubation Time
In-process Monitoring	Pharmaceutical ingredient bioburden	48–72 hours (Total Aerobic Microbial Count) or 5–7 days (Total Combined Yeast & Mold Count)
	In-process intermediate bioburden testing	As above
	Environmental monitoring	As above
	Water monitoring	2–5 days (Total Aerobic Microbial Count)
	Cleaning validation or verification	As above
Product Testing	Sterility testing	14 days
	Microbial limits testing	48–72 hours (Total Aerobic Microbial Count) or 5–7 days (Total Combined Yeast & Mold Count)
	Bacterial endotoxin test	90 minutes
	Microbial assay of vitamins and antibiotics	18–24 hours
	Microbial identification	3–14 days

Clearly the extended incubation times of the current microbial tests preclude them from being applied to PAT. Furthermore, optimization of the manufacturing process and the substitution of in-process chemical and physical monitoring to reduce the product manufacturing and release cycle will not be possible when the in-process and product release microbial testing are the most lengthy parts of the cycle. For example, the bulk solution preparation, sterile filtration, and aseptic filling of sterile pharmaceutical product may take 1–2 days, while the sterility test has an incubation time of 14 days. The advent of RMMs that are less reliant on microbial growth represent a major opportunity to reduce the risk of microbial contamination and shorten the product release cycle time.

The PDA Task Force conveniently classified microbiological testing methods as 1) growth-based, 2) viability-based, 3) cellular component– or artifact-based, and 4) nucleic acid–based methods (*3*). Growth-based methods rely on the measurement of biochemical, physiological, or physical parameters that reflect the growth of the microorganisms; hence they will never be real-time methods. Conventional examples of growth-based microbial testing technologies are plate count, most probable number multiple-tube, and membrane filtration methods. Rapid microbiology examples of growth-based microbial testing technologies are ATP bioluminescence, impedance, and colorimetric or radiometric CO_2 detection methods. The commercialization of highly sensitive image analyzers has made it possible to count microbial colonies on plates before they develop into visual colonies, eliminating lengthy incubation time (updating Frost's Little Plate Count Method.)

Some examples of viability-based methods are:

- Direct epifluoroscence microscopy; the microbial cells are detected on a membrane filter using vital staining and epifluorescence microscopy
- Solid-phase laser scanning fluorescence microscopy; microbial cells that are collected on a membrane filter transport a fluorogenic substrate into their cells and enzymatically cleave the nonfluorescent substrate. A fluorochrome is released and accumulates within the cells and is detected by laser-induced fluorescence
- Flow fluorescence cytometry that employs similar chemistry in a highly sensitive flow cytometer.

Some examples of artifact-based methods are:

- Fatty acid profile analysis using gas chromatography for microbial identification
- Charged molecular weight profiles from intact microbial cells using MALDI-TOF mass spectrometry for microbial identification
- Fluorescence antibody techniques for specific microbial cell detection and enumeration
- The Bacterial Endotoxin—*Limulus* Amebocyte Lysate Test.

Nucleic acid–based methods that are most closely associated with microbial identification include DNA hybridization, ribotyping, and 16S rRNA sequencing techniques. Recent advances in Polymerase Chain Reaction (PCR) technology make it possible to use rapid cyclers and specific primers to amplify and use fluorescence-tagged probes to detect microbial nucleic acids in real time. It is possible to achieve up to 48 amplification cycles within 20 minutes—the same time required for a single generation for a dividing microbial cell. It is technically possible to semi-quantify specific microorganisms within a test sample using this

technology. For example, the log magnitude of Gram-negative bacteria within a water sample can be determined using PCR technology based on the number of amplification cycles to reach a predetermined quantity of nucleic acid.

The challenge for a microbiologist within the PAT initiative will be identify critical processing steps in a manufacturing process for a particular pharmaceutical dosage form and to apply an RMM to monitor the bioburden within the product intermediate to control the process and lessen the risk of microbial contamination. Several risk assessment programs could be applied, including: Hazard Analysis and Critical Control Points (HACCP) from the food industry, and Failure Mode and Effects Analysis (FMEA), an engineering program. The system developed by the food industry has general applicability to microbial contamination in the pharmaceutical industry. In the 1960s, the Pillsbury Company, the U.S. Army, and NASA introduced a system for ensuring pathogen-free foods for the space program. This system, HACCP, focuses on critical food safety areas as part of total quality programs and has been implemented by FDA to prevent microbial contamination of foodstuffs at risk to cause food-borne microbial illness (*4*). It involves a critical examination of the entire food manufacturing process to determine every step at which there is a possibility of physical, chemical, or microbiological contamination of the food, which would render it unsafe or unacceptable for human consumption. These identified points are the critical control points (CCP).

There are seven principles to HACCP:

1. analyze hazards
2. determine CCPs
3. establish critical limits
4. establish monitoring procedures
5. establish deviation procedures
6. establish verification procedures
7. establish record-keeping procedures.

Process steps for the manufacture of a sterile injectable pharmaceutical drug are:

1. Procurement of pharmaceutical ingredients
2. Warehousing pharmaceutical ingredients
3. Incoming microbial testing of pharmaceutical ingredients
4. Batching of the pharmaceutical ingredients
5. Preparation of Water for Injection
6. Bulk solution equipment cleaning
7. Bulk solution preparation and release
8. Container and closure preparation, depyogenation, and sterilization
9. Aseptic filling equipment cleaning and sterilization
10. Clean room cleaning and sanitization
11. Personnel gowning and entry
12. Sterile filtration
13. Aseptic filling, capping, and sealing
14. Air, personnel, and facilities microbial monitoring
15. Product inspection
16. Quality attributes testing
17. Batch record review and deviation investigation
18. Product release.

From a microbiological testing aspect the five critical process steps are a) incoming microbial testing of pharmaceutical ingredients (Step 3), b) preparation of Water for Injection (Step 5), c) bulk solution preparation and sterile filtration (Step 7), d) air, personnel, and facilities microbial monitoring (Step 14), and e) quality attributes testing (Step 16).

An example of the application of FMEA to the pharmaceutical industry may be found in a case study of risk associated with the routine use of sterility testing isolators (*5*). A numerical approach was employed based on 1) severity, i.e., the consequence of failure, 2) occurrence, i.e., the likelihood of failure based on past experience, and 3) detection, i.e., the monitoring system in place and likelihood that the monitoring system will detect a failure. The critical areas investigated were the room surrounding the isolator, the decontamination cycle, the frequency of decontamination, isolator integrity, transfer of material from the transfer isolator to the testing isolator, incomplete sample and equipment decontamination, and isolator operating parameter failure. The risk assessment identified glove leaks, loss of isolator integrity, and incomplete decontamination as the greatest risks, in descending order.

Because the formal application of risk assessment techniques to pharmaceutical processes is a new activity, the reader is cautioned to avoid the uncritical transfer of techniques from other industries to the pharmaceutical industry. The authors hope that unique intellectual frames for risk assessment in the pharmaceutical industry are developed and incorporate the specific requirements of pharmaceutical manufacturing and testing processes.

The question may be asked, if RMMs were available could they be beneficially deployed for process monitoring to establish CCPs? Clearly RMMs may be employed for the incoming microbial testing of pharmaceutical ingredients, for product release testing to reduce the manufacturing and release cycle time and control inventories, and to prevent product backorders. Because in-line conductivity and total organic carbon measurements are being employed for real-time monitoring of water for pharmaceutical purposes, it would be attractive to add in-line microbial monitoring as a control for these important pharmaceutical ingredients. Fluorescence flow cytometry may be a potential candidate for this function. The presterile filtration bioburden is a critical parameter for the maintenance of a high level of sterility assurance of aseptically filled pharmaceutical products. A real-time measurement of the number and size of bacteria within the bulk solution could control the bacterial challenge to the sterilizing filter. However, first an appropriate bioburden level for a specified bulk solution volume and sterilizing filter surface area should be determined. It is assumed that the alert and action levels would be related to the recommended microbial count for bulk Water for Injection and the sterilizing filter rating of the retention of 10^7 colony-forming units of the challenge organism, *Brevundimonas diminuta,* per square cm of filter surface (*6*). An RMM that can produce microbial counts within 1–3 hours could be employed as a process control

providing information prior to starting the sterile filtration process. An RMM could be employed as a cleaning verification step for critical equipment and facilities. In response to bioterrorism threats, research organizations and commercial companies are working on optical laser microbial detection systems that could conceivably be used for real-time monitoring of air and surfaces in aseptic processing areas. Time will tell whether these technologies will have utility in the pharmaceutical industry.

Performing routine microbial monitoring to demonstrate a satisfactory level of process control and identify adverse trends during sterile product manufacturing takes considerable effort. Much of this effort is wasted because of the delay in obtaining microbial testing results and our inability to analyze the data and recognize adverse trends in a timely manner. Major benefits would arise from combining information technology and instrumentation for microbial detection, enumeration, and identification. These would include electronic data capture and the ability to analyze the data in real time to quickly identify adverse trends. Most microbial tests are limit tests. Examples of limit tests are: an absence of *E. coli* in 10 g of a pharmaceutical ingredient, less than 10 colony-forming units in 100 mL of Water for Injection, or less than 1 colony-forming unit in 10 cubic feet of air in a Grade A aseptic processing area. Unlike chemical assays for potency in which simple control charts can identify changes in the manufacturing process, the vast preponderance of microbial test results are below the sensitivity of the test. This makes the real-time capture and analysis of the test results more important with the employment of trend rules that are not immediately obvious on inspection of the data. Examples of these rules may be the frequency of out-of-limit results within an extended time period or the mean time between occurrences of rare events.

Given the potential benefits of RMMs in PAT what are the major obstacles to their development, validation, and implementation?

Obstacles include:

- New microbial testing technologies that do not deliver on their promise in terms of standardized testing methods
- The inability of pharmaceutical microbiologists to evaluate and select methods appropriate for a particular application
- The lack of consensus on how to validate RMMs and demonstrate their equivalency to compendial test methods
- Disagreement about the acceptability of defaulting from the alternative RMM to the compendial tests when an out-of-specification result is obtained
- Pharmaceutical companies' being regulatory-risk adverse
- Higher capital and unit testing costs
- Lack of serious commitment to RMM by the pharmaceutical industry, and
- Past lack of leadership regarding the PAT initiative from regulatory agencies.

How are these obstacles to be met? Companies developing RMMs must work closely with opinion leaders in the pharmaceutical industry to develop applications that can be implemented. Microbiologists need to revisit the concepts contained in the PDA Technical Report No. 33 The Evaluation, Validation, and Implementation of New Microbiological Testing Methods (*3*) and the USP In-Process Revision Validation of Alternative Microbial Methods (*7*) as they may be too confined to *USP–NF* ⟨1225⟩ *Validation of Compendial Methods* (*8*). The acceptance criterion of same or better recoveries than the compendial method may be too rigid. RMMs will differ in their selectivity in the recovery of a microbial population and thus will have a high bias with respect to microbiological growth–based methods. RMMs that have different units of measurement should be evaluated to determine if new control criteria (for pass/fail or alert/action levels) are warranted. An example is the difference between classic culture methods reported as colony-forming units and viable but not culturable microbial cells with solid phase laser scanning fluorescence microscopy. The results obtained by different enumeration methods should be compared to the existing requirements and evaluated against microbial risk for a particular pharmaceutical dosage form. For example, water microbiological standards are based on microbiological culture methods. The health impact of a potable water system would not change if higher microbial counts were obtained using a microbial enumeration method that counted microorganisms that do not grow on microbiological media unless there was compelling epidemiological evidence that higher microbial counts obtained by an RMM had public health consequences. The same argument can be made for water for pharmaceutical purposes.

Appropriate planning and detail can begin to develop an approach that is scientifically sound. One approach, using comparability (FDA Guidance, February 2003, Comparability Protocols—Chemistry, Manufacturing, and Controls Information) may be an acceptable way to justify changing test methodology from a classical method to an RMM. Key details that could be included in the comparability protocol are: instrument validation (design qualification, installation qualification, and operational qualification), tests to perform and criteria to meet to indicate equivalency within the capability of the two methods compared, and plans for periodic reporting to regulatory authorities if changes occur after implementation of the RMM.

Microbiologists need to convince their companies that an investment in RMMs will result in inventory reductions, fewer product failures, faster resolution of laboratory and manufacturing investigations, and better product quality.

There are now movements within industry and the regulatory agencies to collaborate and to develop acceptance criteria and to open avenues for changing to RMMs in an environment where technology can enhance analytical measurement in real time, providing increased assurance of product quality.

REFERENCES

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8. *USP–NF* ⟨1225⟩ *Validation of Compendial Methods.*

NOMENCLATURE

This section includes supplements to the latest edition of the *USP Dictionary of USAN and International Drug Names* that incorporate new United States Adopted Names (USAN) and revisions to existing Dictionary names. Also listed are Proposed and Recommended International Nonproprietary Names (INN) when they have been announced by the World Health Organization.

Possible names suggested for use as USAN and INN are listed for public review and comment along with information on how nonproprietary names are devised. In addition, readers may find articles relevant to current compendial nomenclature issues that also occasionally report on related matters pertaining to USAN and INN.

USP Dictionary of USAN and International Drug Names
2003 USP DICTIONARY SUPPLEMENT 4

IMPORTANT—Save this Supplement. This and all supplements appearing in *PF* are needed to keep the 2003 edition of the USP Dictionary (USPD) up to date. The cumulative contents of the supplements to the current (2003) edition will be included in the next complete edition of the Dictionary.

New United States Adopted Names (USAN)

No newly established United States Adopted Names (USAN) are available for publication at this time. See preceding and succeeding numbers of *PF* for other new USAN to supplement the Dictionary main volume.

Revisions of United States Adopted Names (USAN)

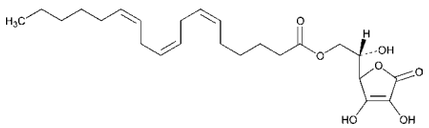
The following are revisions of existing United States Adopted Names (USAN) and other names.

Antimony Trisulfide Colloid

Change the chemical structure to read:

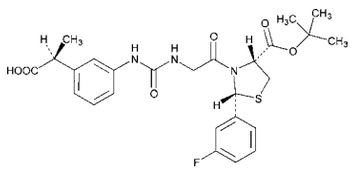
Ascorbyl Gamolenate

Change the chemical structure to read:



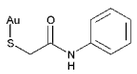
Aseripide

Change the chemical structure to read:



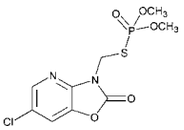
Aurothioglycanide

Change the chemical structure to read:



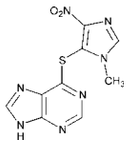
Azamethiphos

Add the following chemical structure:



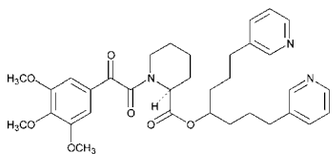
Azathioprine

Change the chemical structure to read:



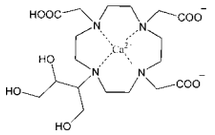
Biricodar

Change the chemical structure to read:



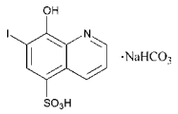
Calcobutrol

Change the chemical structure to read:



Chiniofon

Change the chemical structure to read:



Proposed and Recommended International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO).

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

Recommended International Nonproprietary Names

The following 57 nonproprietary names have been selected by the World Health Organization (WHO) as Recommended International Nonproprietary Names. This list, with chemical names or descriptions and the molecular formulae, appears in *WHO Drug Information*, Vol 17, No. 2, 2003.

Recommended INN	Recommended INN	Recommended INN	Recommended INN
Albaconazole	Ertiprotafib	Naminidil	Soraprazan
Alvimopan	Eszopiclone	Nemifitide	Tapentadol
Apaziquone	Fandosentan	Nortopixantrone	Tecadenoson
Apolizumab	Fontolizumab	Oblimersen	Tecalcet
Asenapine	Garenoxacin	Ortataxel	Teneliximab
Axomadol	Inecalcitol	Osemozotan	Topixantrone
Bifeprunox	Iroxanadine	Pascolizumab	Toralizumab
Canertinib	Lidorestat	Pegaptanib	Torcetrapib
Cefovecin	Liraglutide	Pegsunercept	Torcitabine
Cethromycin	Lubiprostone	Perflubrodec	Treprostinil
Dabigatran Etexilate	Lumiracoxib	Picoplatin	Triplatin Tetranitrate
Ecromeximab	Merimepodib	Plevitrexed	Tulathromycin
Eculizumab	Mozavaptan	Pumosetrag	Vapaliximab
Elzasonan	Nalfurafine	Siplizumab	Varespladib
Enecadin			

Suggested United States Adopted Names

The United States Adopted Names (USAN) program is the specifically organized effort in the United States directed to producing simple and useful nonproprietary names for drugs while the drugs are still in the investigational stages. The American Medical Association (AMA), the American Pharmaceutical Association (APhA), and the United States Pharmacopeial Convention (USPC) jointly sponsor the USAN program with representation from the FDA.

Each U.S. Adopted Name is chosen with the expectation that it will be suitable for prescribing and dispensing purposes and for designation as the title of the monograph, should the article be recognized in the official *United States Pharmacopeia* or *National Formulary.* A measure of the prestige and recognition of the value of the USAN program can be found in the following regulations published by the Commissioner of Food and Drugs and the Secretary of Health and Human Services in the *Federal Register* of February 1988.

> All who are concerned with the prescription, dispensing, use, sale or manufacture of drugs may, in the absence of the designation of an official name by the FDA, rely on the current compendial name or the U.S. Adopted Name (USAN) listed in this volume as being the established name in accordance with the Federal Food, Drug, and Cosmetic Act.

A formal procedure[1] is followed by the USAN Council in selecting an established name for a drug. The USAN Council Secretary is also an ex officio member of the International Nonproprietary Names (INN) Committee. USAN Guiding Principles are concordant with World Health Organization (WHO) principles, and all USANs for substances also named by the INN Committee are systematically processed through the INN Committee. This ensures that, with very rare exceptions, USANs are identical to INNs and available for world-wide use.

A suggestion for a USAN originates usually from a firm or an individual who has developed a substance of potential therapeutic utility to the point where there is a distinct possibility of its being marketed in the United States of America. Occasionally, the initiative is taken by the USAN Council in the form of a request to parties interested in a substance for which a nonproprietary name appears to be lacking.

Submissions to the USAN Council are expected to conform to the established Guiding Principles[2] and to be reasonably free from conflict with other names, including both trademarks and nonproprietary names. An effort is made to discourage the occasional, undesirable practice of incorporating in trademarks the syllables used in an established nonproprietary name, or syllables recommended for USAN. Such trademarks may act as a bar to the subsequent adoption of appropriate nonproprietary names for closely related drugs.

The suggested nonproprietary names for the drugs described in the following list are under consideration by the USAN Council. The name(s) being considered for each drug substance, and the applicable *category*, are separated by double spacing from the name(s) and *category* for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Suggested USAN	Category
Abatapcept Alfa Abatapcim Alfa Abatapcimus Alfa Abatapfusim Alfa Signatapcim Alfa Signatapcimus Alfa	*Treatment of autoimmune diseases*
Abrextrin Apiclermin Aplicermin Aprexermin Aprextrin Daprexermin	*Treatment of obesity*
Abrimostim Lanimostim	*Antineoplastic*
Abtumumab Aclatumumab Atumumab Hutumumab Paritumumab Ulatumumab	*Antineoplastic*
Abubucol Abucolide Libobucol Lobucolide Resibucol	*Prevention of chronic solid organ transplant rejection*
Acalcidiol Acalcisecodiol Becocalcidiol Nobicalcidiol Secocalcidiol	*Treatment of psoriasis*
Aclogrel Hydrochloride Cicloflugrel Hydrochloride Flosulagrel Hydrochloride Losulagrel Hydrochloride Prasugrel Hydrochloride Prasulagrel Hydrochloride Prosulagrel Hydrochloride Prosulgrel Hydrochloride	*Platelet aggregation inhibitor*
Acrimustivir Dihydrochloride Acromustine Dihydrochloride Acromustrale Dihydrochloride Afralemust Dihydrochloride Amustaline Dihydrochloride Amustalino Dihydrochloride Cloracrilink Dihydrochloride Crilomustine Dihydrochloride Linomustine Dihydrochloride	*Red blood cell pathogen activation*

[1] *USP Dictionary of USAN and International Drug Names,* Preface.

[2] Ibid., Appendix VII.

Suggested USAN	Category
Adafaxine Hydrochloride	*Antidepressant; antianxiety*
Aldafaxine Hydrochloride	
Atafaxine Hydrochloride	
Edanfaxine Hydrochloride	
Efdanfaxine Hydrochloride	
Sunefaxine Hydrochloride	
Vadafaxine Hydrochloride	
Zunefaxine Hydrochloride	
Advapladib	*Treatment of pain and symptomatic management of arthritis*
Arapladib	
Avapladib	
Efipladib	
Tarapladib	
Adv-2,5-huE1B-deleted-2	*Antineoplastic*
Adv-2,5-hup53-2	
Ixadusugene (E1B deleted)	
Ixadusugene (p53)	
Lontucirev (Replicating Adenovirus)	
Padtucirev (Replicating Adenovirus)	
Afenaticib	*Treatment of rheumatoid arthritis*
Afenatastat	
Fapenatacib	
Fapenetacib	
Rafatacib	
Rafenatacib	
Rafutastat	
Afglucosidase Alfa	*Treatment of Pompe disease*
Aglucosidase Alfa	
Alglucosidase Alfa	
Alglucosidase Beta	
Agaglitacor	*Antidiabetic; antidyslipidemic*
Atraglitazar	
Onaglitazar	
Optiglitacor	
Sivaglitazar	
Siviglitacor	
Sonaglitacor	
Sonaglitazar	
Sonaglitazet	
Sonaglitazone	
Alaglumetad Hydrochloride	*Treatment of general anxiety disorders and smoking cessation*
Eglumetad Alanine Hydrochloride	
Talaglumetad Hydrochloride	
Xalaglumetad Hydrochloride	
Alimepodib	*Treatment of psoriasis and multiple sclerosis*
Dimepodib	
Primepodib	
Trimepodib	
Aloglustratide	*Antineoplastic*
Canglustratide	
Talaglustract	
Tzalapotide	
Ancripentoc	*Antiviral; immunomodulator*
Broxicicra	
Metirafiv	
Queviracir	
Queviracrent	
Quevircirant	
Quicrentevir	
Quintacirin	
Racirfivant	
Ranticicra	
Ranticicrant	
Ranticirpant	
Rantirafiv	
Viracirin	
Zeptacirin	
Anretinib	*Antineoplastic*
Arcutinib	
Palrotinib	
Panretinib	
Pelritinib	
Ramotinib	
Recetinib	
Apoptaxel	*Antineoplastic*
Azetaxel	
Milataxel	
Aquifocon A	*Hydrophobic contact lens material*
Aquilafocon A	
Aquilfocon A	
Aquilofocon A	
Arblurbifenil	*Treatment of Alzheimer's disease*
Arflurbifenil	
Arflurbifenpro	
Arflurbinifen	
Arflurbiprofen	
Flurbifenil	
Artagoxoforb	*Antineoplastic*
Bariloxoforb	
Barilubant	
Eitagoxoforb	
Etagolokib	
Etagoloxan	
Etagolubant	
Etagolukib	
Etalokib	
Etalubloxan	
Igolubant	
Tagolubant	
Asterbulin	*Chemotherapeutic agent for solid tumors; tubulin inhibitor*
Atrobulin	
Mivobulin	
Taltobulin	
Tubulastin	
Xenobulin	
Atamcimod Acetate	*Treatment of chemotherapy-induced diarrhea (CID)*
Binamcimod Acetate	
Delamcimod Acetate	
Delamgatide Acetate	

Suggested USAN	Category
Atilizumab	*Monoclonal antibody*
Atlizumab	
Nealizumab	
Nelizumab	
Noralizumab	
Tocilizumab	
Avicurium Chloride	*Neuromuscular blocker*
Bantacurium Chloride	
Benecurium Chloride	
Bravacurium Chloride	
Brevicurium Chloride	
Brosacurium Chloride	
Gantacurium Chloride	
Nexicurium Chloride	
Revacurium Chloride	
Vantacurium Chloride	
Velocurium Chloride	
Zelacurium Chloride	
Barfusakinra	*Treatment of rheumatoid arthritis*
Benfusakinra	
Binakinra	
Kinakinra	
Setfunakinra	
Setfusakinra	
Beclabucol	*Reduction of signs and symptoms and inhibition of progressive structural damage in patients with mild to severe rheumatoid arthritis*
Cetabucol	
Glibucolide	
Glidobucol	
Glybucolide	
Becorotan Hydrochloride	*Treatment of Alzheimer's disease*
Becorotane Hydrochloride	
Lecorotan Hydrochloride	
Lecorotane Hydrochloride	
Lecozotan Hydrochloride	
Lecozotane Hydrochloride	
Bectapitant Mesylate	*Antiemetic*
Vestipitant Mesylate	
Vintapitant Mesylate	
Bepisermin	*Antidiabetic*
Cobasermin	
Derasermin	
Mecasermin Infabate	
Mecasermin Rinfabate	
Obasermin	
Bioctadekin	*Treatment of disseminated solid tumors*
Idoctadekin	
Immunoctadekin	
Munoctadekin	
Bisurex	*Contraceptive; anti-infective*
Cebemirex	
Cebemirside	
Cemisurex	
Cetamox	
Pamiceb	
Bitafosol Tetrasodium	*Treatment of rhinitis, URI and lung disease, including cystic fibrosis; also retinal detachment and edema*
Denufosol Tetrasodium	
Dinufosol Tetrasodium	
Dipirafosol Tetrasodium	
Dipirfosol Tetrasodium	

Suggested USAN	Category
Cadenoson	*Management of atrial fibrillation and atrial flutter*
Redenoson	
Selodenoson	
Calimumab	*Anti-inflammatory*
Relimumab	
Rolimumab	
Zolimumab	
Zylimumab	
Capaprovir	*Treatment of Hepatitis C infection*
Cepaprovir	
Cepaprovirate	
Ciclocivirate	
Cicloprovirate	
Ciluprevir	
Ciluprovir	
Catelavancin Hydrochloride	*Antibacterial agent*
Catellavancin Hydrochloride	
Selavancin Hydrochloride	
Stenavancin Hydrochloride	
Stenzenvancin Hydrochloride	
Telavancin Hydrochloride	
Cenalidomide	*Antineoplastic*
Centroxidomide	
Cenzoxamide	
Cetroxidomide	
Enazalidomide	
Cixicirfor	*Stem cell mobilization*
Ericixafor	
Ericixcrant	
Ericixirfor	
Contafocon A	*Hydrophobic contact lens material*
Contafocon B	*Hydrophobic contact lens material*
Contafocon C	*Hydrophobic contact lens material*
Contafocon D	*Hydrophobic contact lens material*
Contafocon E	*Hydrophobic contact lens material*
Criselestat	*Treatment of bronchopulmonary inflammatory damage, specifically cystic fibrosis*
Didelestat	
Epelestat	
Epelestatal	
Dabuzalgron Hydrochloride	*Treatment of stress urinary incontinence*
Dasantafil	*Treatment of erectile dysfunction*
Vasantafil	
Zoranafil	
Denesbuvir	*Treatment of Hepatitis C*
Epanesbuvir	
Nesbuvir	

Suggested USAN	Category
Didenoson Duodenoson Flodenoson Parmodenoson Regadenoson Regodenoson	*Coronary vasodilator for intravenous use as an adjunct or pharmacologic stress agent, in radionuclide myocardial perfusion imaging in patients unable to exercise adequately*
Didroequol Didronoxel Didronoxil Idrodequol Idroequol Idronoxil Phenoxodiol	*Antineoplastic*
Disufenton	*Neuroprotective agent used to treat ischemic stroke*
Eglumetad	*Treatment of anxiety and stress disorders*
Eltrombopan Diolamine Etrobopan Diolamine Gemcaristim Getrobopan Diolamine Megprocaristim Recepcaristim Retrombopan Diolamine Xelcaristim Zexcaristim	*Treatment of thrombocytopenia and idiopathic thrombocytopenic purpura*
Epicallantide Epicallide Epicallintide Epikallintide	*Plasma kallikrein inhibitor*
Eriforan Eritolforan Eritolimod Lipoforan	*Treatment of sepsis*
Etemucret Idroxicotrent	*Treatment of dry eye*
Ezadenosant Ezadenoson Ispredenosant Sodenosant Xodenosant Xodenoson Zadenosant	*Adenosine 2a receptor antagonist intended for use in treatment of Alzheimer's disease*
Fexifotel Perzinfotel Veramafotel Veramfotel	*Treatment of neuropathic pain*
Human Secretin Secretin Secretin (Human) Secretin (Humanized)	*Diagnostic aid, specifically stimulation of pancreatic secretions*
Inkinesib Mesylate Iskinesib Mesylate Ispinesib Mesylate Kispinesib Mesylate Tokinesib Mesylate Tominesib Mesylate	*Antineoplastic*
Lemuxaporfin Leranaporfin Luxaporfin Ranaporfin Seraporfin Sertaporfin Tuxaporfin	*Photodynamic therapy*
Levtofisopam	*Anxiolytic, autonomic instability*
Linxotecan Pegbetotecan Pegcamotecan Pegcamtecan Peglinxotecan	*Antineoplastic*
Liopixen Melopixen Penapixen	*Treatment of rheumatoid arthritis*
Metazamulin Prusarimulin Retezamulin Tezapimulin Zapimulin	*Topical antibiotic for secondarily infected traumatic lesions (SITL) and secondarily infected dermatoses (SID) or impetigo*
Micafungin Sodium	*Intravenous treatment of fungal infections caused by Aspergillus and Candida species*
Netoglitazone	*Antidiabetic; orally administered insulin action enhancer to lower the plasma glucose in patients with noninsulin dependent diabetes mellitus (type II)*
Paliperidone	*Treatment of schizophrenia*
Paliperidone Palmitate	*Treatment of schizophrenia*
Paltozumab Patocizumab Riabuzumab Ribacizumab Tadocizumab Taidozumab	*Treatment of patients undergoing percutaneous coronary interventions*
Probucol Hemisuccinate Resibucol Succinbucol Sucinbucol Tebucolide	*Antiproliferative; antioxidant*
Produlestan Trodulamine Trodulespan Trodulesqual Trodulestamine Trodulestane Troduspemol Trodusqualine Trodusquemine	*Appetite suppression*
Psyllium (hemicellulose) Psyllium Hemicellulose	*Laxation, cholesterol lowering*

Suggested USAN	Category
Rotigotine	*Treatment of Parkinson's disease and restless legs syndrome*
Selegiline	*Antidepressant*
Senofilcon A	*Hydrophilic contact lens material*
Stabaczumab Stafabaczumab Staphbaczumab Stefibaczumab	*Treatment of Staphylococcus aureus infections*
Tiplactinib Tiplactinin Tiplagtinin Tiplastinin Tiplaxtinin Tiplaxtinor	*Treatment of fibrinolytic impairment*
Trabectedin	*Antineoplastic*
Valmozamide Valmozomide Valrocemide Valtrecemide	*Antiepileptic; anticonvulsant*
Yttrium Y90 Epratuzumab-DOTA Yttrium Y90 Epratuzumab Dotetate Yttrium Y90 Epratuzumab Dotetran Yttrium Y90 Epratuzumab Itrateric	*Radioimmunotherapy (RAIT) for non-Hodgkin's B-cell lymphoma patients*
Yttrium Y90 Lecratuzumab Yttrium Y90 Tacatuzumab Yttrium Y90 Tactuzumab Yttrium Y90 Vintuzumab	*Tumor eradication via selective targeting of APF-positive cancers by radiolabeled hAPF-31*

Suggested International Nonproprietary Names

International Nonproprietary Names (INN) are devised by the World Health Organization (WHO). INNs for substances originating within the United States are applied for through the USAN Council. INN and USAN Guiding Principles are concordant, which assures that, with very few exceptions, INNs and USANs are identical.

Under its charter, the WHO is empowered simply to *recommend* specific actions or procedures to its Member States. This limitation is incorporated into the WHO program concerned with the selection of international nonproprietary names for pharmaceutical substances, in that the WHO first publishes the selected names as *proposals* (''Proposed International Nonproprietary Names''). A period of four months from the date of publication in *WHO Drug Information* is allowed for entering comments on, or objections to, any proposal on the part of Member States or other interested parties. In general, an objection reflects a belief that the proposal concerned is confusingly close to (i.e., conflicts with) a name already in use, perhaps in only a restricted area in which the party has a proprietary interest in the form of trademark rights. In the event that no objection is received, the WHO proceeds with listing and publishing the names so devised as *recommendations* (''Recommended International Nonproprietary Names''), which many Member States then recognize as the sole or preferred nonproprietary name for use within their respective territories.

The names for the drugs that are categorized in the following list are under consideration for the selection of new Proposed International Nonproprietary Names. The name(s) being considered for each drug substance, and the applicable *category*, are separated by double spacing from the name(s) and *category* for the next listed drug substance. Where two or more names are being considered for the same drug substance, the names are single-spaced, and the applicable category term is written only once to the right of the single-spaced group of names.

Any comments or protests should be addressed to Sandra Van Laan, Assistant Secretary, USAN Council, American Medical Association, 515 North State Street, Chicago, Illinois 60610.

Nomenclature

Suggested INN	Category
Accravir Inccravir Kinokemavir Kinovir Noccravir Zenokinovir	*Antiviral*
Alglucosidase Alfa	*Enzyme replacement therapy for the treatment of Pompe's disease*
Alopilone Fantopilone Syopilone	*Treatment of advanced solid tumors*
Amipridadine Eonadine Imipridadine	*Antihistamine*
Amustaline	*Nucleic acid alkylator used in the ex vivo blood bank process for inactivation of virusis, bacteria, parasites, and leukocytes in red blood cells*
Ancripentoc	*Antiviral; immunomodulator*
Apritapix Apritrotapix Pitatroban Tapitroban	*Treatment of myocardial infarction*
Atlizumab Tocilizumab	*Monoclonal antibody*
Besitomab Granulomab Mitrilomab	*Monoclonal antibody*
Biofact Biofactant Folprofact	*Treatment of acute lung injury/acute respiratory distress syndrome*
Botadopa Botagolide Protaline Protiamine Protioline Retadopa Rotigotine	*Antiparkinsonian*
Canglustratide	*Antineoplastic agent*
Cetalistat	*Lipase inhibitor*
Ciluprevir Ciluprovir	*Treatment of Hepatitis C infection*
Cindolamide Indibulin Indobulin Indoxobulin	*Antineoplastic agent*
Dablusagon Dabluzagon Dabuzalgron Zoyanagon	*Treatment of urinary incontinence*
Daprexermin	*Treatment of obesity*
Diphentrone Disphenitrone Disufenton Phenitrone	*Neuroprotectant agent used to treat ischemic stroke*
Disramide Ditocemide Ditopamide Dixibamide Valgabamide Valgabite Valproate Oxedamine Valrocemide	*Antiepileptic; anticonvulsant*

Suggested INN	Category
Ecteinibin Ecteinoturbein Trabectedin Trantiblectein Turbinectein	*Antineoplastic*
Emglumegad Eglumetad	*Antianxiety; Smoking cessation*
Epicallantide	*60 Amino acid protein that has been genetically engineered to inhibit human plasma kallikrein with high affinity and specificity*
Imiglatazar Oxiglitazar	*Antidiabetic*
Indanterol Quindanterol Quinoterol	*Bronchodilator*
Lemuxaporfin	*Photosensitivity agent with applications of photodynamic therapy*
Levtofisopam	*Anxiolytic, autonomic instability*
Mecasermin Obasermin	*Hormone replacement used in the treatment of diabetes*
Micafungin	*Antifungal*
Milataxel	*Antineoplastic agent*
Nesbuvir	*Treatment of Hepatitis C*
Netoglitazone	*Antidiabetic*
Nexfuvirtide Tifuvirtide Zanfuvirtide	*HIV inhibitor for the treatment of HIV infection*
Paliperidone	*Treatment of schizophrenia*
Pelritinib	*Antineoplastic*
Perflisoban Perflisotan Perfluban Perfluroban Perflutan	*Ultrasound contrast agent/diagnostic aid*
Psyllium hemicellulose	*Laxation; cholesterol lowering*
Selodenoson	*Management of atrial fibrillation and atrial flutter*
Sonaglitazar Sonaglitazone	*Antidiabetic; Antidyslipidemic*
Taltobulin	*Treatment of solid tumors*

Nomenclature

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New Items at a Glance

See what's new in USP Reference Standards. For your convenient and quick reference, here 's a list of Reference Standards released by USP over the past year.

This list is continuously updated with the newest Reference Standards released within the past 12 months.

Cat.No.	Description	Curr. Lot	Price
1002505	Acesulfame Potassium (200 mg)	F0C136	$250
1012780	Alendronate Sodium (200 mg)	F0B315	$150
1012939	Allantoin (200 mg)	F0C169	$150
1019417	Amifostine Disulfide (25 mg)	F0C152	$468
1025908	Aminopentamide Sulfate (200 mg)	F0B273	$150
1028000	Amitraz (200 mg)	F0C042	$150
1029953	Ammonium Chloride (200 mg)	F0C134	$150
1043750	Aspartame Acesulfame (200 mg)	F0C137	$150
*1048620	Benazapril Related Compound A (15 mg)	F0C252	$468
*1048630	Benazapril Related Compound B (15 mg)	F0C256	$468
1065618	Betahistine Hydrochloride (200 mg)	F0C105	$150
1076363	Brinzolamide (200 mg)	F0C034	$150
1076374	Brinzolamide Related Compound A (50 mg)	F0C033	$468
1076385	Brinzolamide Related Compound B (50 mg)	F0C035	$468
1078733	Bupropion (200 mg)	F0C123	$200
1097636	Cefepime Hydrochloride (500 mg)	F0C063	$150
1097647	Cefepime Hydrochloride System Suitability (25 mg)	F0C095	$150
1103105	Cetyl Palmitate (50 mg)	F0B241	$150
1133536	Choline Bitartrate (200 mg)	F0C057	$150
1133547	Choline Chloride (200 mg)	F0C058	$150
1133570	Chondroitin Sulfate Sodium (300 mg)	F0B256	$150
1140247	Clomipramine Hydrochloride (200 mg)	F0C075	$150
1142107	Clozapine (100 mg)	F0C032	$250
1148500	Copovidone (100 mg)	F0C194	$150
*1171900	Desflurane (0.5 mL)	F0C187	$150
1171910	Desflurane Related Compound A (0.1 mL)	F0C031	$468
1173235	Desogestrel (50 mg)	F0B282	$150
1173246	Desogestrel Related Compound A (15 mg)	F0B279	$468
1173257	Desogestrel Related Compound B (15 mg)	F0B284	$468
1173268	Desogestrel Related Compound C (25 mg)	F0B281	$468
*1179708	Dextran 40 (50 mg)	F0C247	$150
*1179741	Dextran 70 (50 mg)	F0C260	$150
1179854	Dextran 4 Calibration (100 mg)	F0C002	$150
1179865	Dextran 10 Calibration (100 mg)	F0C010	$150
1179876	Dextran 40 Calibration (100 mg)	F0C011	$150
1179887	Dextran 70 Calibration (100 mg)	F0C013	$150
1179898	Dextran 250 Calibration (100 mg)	F0C039	$150
1179800	Dextran Vo Marker (100 mg)	F0B242	$150
1204805	Diloxanide Furoate (200 mg)	F0C026	$150
1213103	Dinoprostone (50 mg)	F0C030	$1,466
1225281	Dorzolamide Hydrochloride (500 mg)	F0C040	$150
1225292	Dorzolamide Hydrochloride Related Compound A (20 mg)	F0C068	$468
1225419	Doxazosin Mesylate (200 mg)	F0C079	$150
1234806	Emedastine Difumarate (100 mg)	F0C059	$150
1260012	Ethinyl Estradiol Related Compound A (20 mg)	F0B252	$468
1269458	Fenoldopam Mesylate (200 mg)	F0C125	$150
1269469	Fenoldopam Related Compound A (20 mg)	F0C124	$468
1269470	Fenoldopam Related Compound B (20 mg)	F0C126	$468
*1273808	Flumazenil (200 mg)	F0C305	$750
1286060	Formononetin (50 mg)	F0C196	$500
1286366	Fosphenytoin Sodium (250 mg)	F0C156	$150
1287675	Gadoversetamide (200 mg)	F0C172	$150
1287686	Gadoversetamide Related Compound A (200 mg)	F0C173	$468
*1288306	Ganciclovir (200 mg)	F0C287	$350
1288510	Gemfibrozil Related Compound A (20 mg)	F0C101	$468
1291708	Powdered Asian Ginseng Extract (1.5 g)	F0B289	$500
1294976	Glutamic Acid (200 mg)	F0C069	$150
1294808	Glutamine (100 mg)	F0B244	$150
1295888	Glycyrrhizic Acid (25 mg)	F0C006	$468
1315012	Hydrocodone Bitartrate Related Compound A **CII** (70 mg)	F0C214	$493
1329709	Hydroxypropyl Betadex (200 mg)	F0B295	$150
1343517	Iodixanol (200 mg)	F0B240	$150
1343540	Iodixanol Related Compound C (25 mg)	F0B236	$468
1343550	Iodixanol Related Compound D (50 mg)	F0B231	$468
1343561	Iodixanol Related Compound E (25 mg)	F0B229	$468
1348907	Isoflupredone Acetate (200 mg)	F0C109	$150
1355709	Powdered Kava Extract (1 g)	F0C161	$250
1355753	Kawain (200 mg)	F0C160	$200
1356020	Ketamine Related Compound A (50 mg)	F0C118	$468
1356916	Lansoprazole (200 mg)	F0B310	$150
1356927	Lansoprazole Related Compound A (25 mg)	F0B311	$468
1370611	Lovastatin Related Compound A (20 mg)	F0B235	$468
1370906	Lynestrenol (20 mg)	F0B314	$195
1443850	Powdered Milk Thistle Extract (250 mg)	F0B321	$250
1392454	Meropenem (300 mg)	F0C201	$175
1396309	Metformin Hydrochloride (200 mg)	F0C209	$175
1396310	Metformin Related Compound A (50 mg)	F0C210	$468
1443908	Milrinone (500 mg)	F0C050	$250
1443919	Milrinone Related Compound A (50 mg)	F0C051	$468
1445481	Monensin Sodium (200 mg)	F0B293	$150
1449518	Nabumetone (200 mg)	F0C072	$150
1471914	Norgestimate (200 mg)	F0C086	$150
1478582	Ondansetron Hydrochloride (300 mg)	F0C222	$200

17 completely NEW Reference Standards this month! (Look for items marked *)

New Items at a Glance

Cat.No.	Description	Curr. Lot	Price
1478593	Ondansetron Related Compound A (50 mg)	F0C191	$468
1478618	Ondansetron Related Compound C (50 mg)	F0C251	$468
1478629	Ondansetron Related Compound D (50 mg)	F0C226	$468
1482207	Oxaprozin (200 mg)	F0C115	$150
1483301	Oxfendazole (200 mg)	F0C128	$150
1491332	Paclitaxel (200 mg)	F0C180	$1,450
1491343	Paclitaxel Related Compound A (20 mg)	F0C179	$725
1491354	Paclitaxel Related Compound B (20 mg)	F0C181	$725
1500218	Paroxetine Hydrochloride (500 mg)	F0B288	$150
*1500251	Paroxetine Related Compound D (15 mg)	F0C228	$468
1535019	Phenytoin Related Compound A (50 mg)	F0C155	$468
1546106	Poloxalene (500 mg)	F0C009	$150
1593412	Quinapril Related Compound A (50 mg)	F0C114	$468
1593423	Quinapril Related Compound B (50 mg)	F0C116	$468
1596807	Quinine Hydrochloride (1 g)	F0C108	$150
1598303	Ramipril (200 mg)	F0C099	$150
1598314	Ramipril Related Compound A (20 mg)	F0C100	$468
*1599500	Powdered Red Clover Extract (500 mg)	F0C188	$250
1600813	Repaglinide (200 mg)	F0B265	$150
1600824	Repaglinide Related Compound A (50 mg)	F0B267	$468
1600835	Repaglinide Related Compound B (50 mg)	F0B269	$468
1600846	Repaglinide Related Compound C (25 mg)	F0B271	$468
*1612540	Sevoflurane (1 mL)	F0C219	$150
*1612550	Sevoflurane Related Compound A (0.2 mL)	F0C261	$468
1614669	Sodium Starch Glycolate (400 mg)	F0C087	$150
*1617408	Sotalol Hydrochloride (300 mg)	F0C234	$175
*1617419	Sotalol Related Compound A (50 mg)	F0C235	$468
*1617420	Sotalol Related Compound B (50 mg)	F0C236	$468
*1617430	Sotalol Related Compound C (50 mg)	F0C237	$468

Cat.No.	Description	Curr. Lot	Price
*1621507	Stearoyl Polyoxyglycerides (100 mg)	F0C286	$150
1642154	Sumatriptan (50 mg)	F0C220	$200
1642201	Sumatriptan Succinate (200 mg)	F0C231	$200
1642212	Sumatriptan Succinate Related Compound A (15 mg)	F0C221	$600
1642223	Sumatriptan Succinate Related Compound C (50 mg)	F0C230	$600
1642700	Tacrine Hydrochloride (500 mg)	F0C119	$150
1643361	Taurine (100 mg)	F0C104	$150
1643452	Terazosin Hydrochloride (200 mg)	F0C244	$150
1643463	Terazosin Related Compound A (50 mg)	F0C245	$468
1643474	Terazosin Related Compound B (50 mg)	F0C218	$468
1643485	Terazosin Related Compound C (25 mg)	F0C257	$468
1652500	Thalidomide (200 mg)	F0C107	$175
1667359	Tiletamine Hydrochloride (200 mg)	F0C019	$150
1667520	Tinidazole (200 mg)	F0C093	$150
1667530	Tinidazole Related Compound A (100 mg)	F0C091	$468
1703805	Tylosin (250 mg)	F0C008	$150
1706701	Urea C 13 (100 mg)	F0C078	$175
1708773	Valsartan Related Compound A (20 mg)	F0C215	$600
1708795	Valsartan Related Compound C (10 mg)	F0C208	$600
1711461	Verteporfin (200 mg)	F0C166	$150
1711472	Verteporfin Related Compound A (50 mg)	F0C167	$468
*1714506	Vinorelbine Tartrate (200 mg)	F0C243	$150
1714528	Vinorelbine Related Compound A (25 mg)	F0C242	$468
1717708	Vitexin (30 mg)	F0C142	$500
1724656	Zileuton (150 mg)	F0C062	$150
1724667	Zileuton Related Compound A (50 mg)	F0B316	$468
1724678	Zileuton Related Compound B (50 mg)	F0B313	$468
1724689	Zileuton Related Compound C (50 mg)	F0B299	$468

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NOTICE TO THE EXECUTIVE SECRETARIAT OF INTENT TO COMMENT

Date _____

Mail to: Executive Secretariat, USP–NF
12601 Twinbrook Parkway
Rockville, MD 20852

Title(s)	With Reference to the Proposal(s) in *Pharmacopeial Forum:* Vol.	No.	Page(s)	Estimated Date of Sending Comments*

I am unable to comment at present, but please be informed of my intent to comment later, as indicated above.

Name _____
(Please type or print)

Company _____

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*NOTE—Specifying date(s) when you expect to submit comments to the Executive Secretariat will not necessarily result in a deferment of the implementation of the proposal(s) referred to.

[*Please fold before mailing.*]

CHROMATOGRAPHIC REAGENTS USED IN *USP–NF* AND *PHARMACOPEIAL FORUM*

This is an update based on the proposals published in this issue of *PF*.

Chromatographic Reagents Used in *USP–NF* and *Pharmacopeial Forum*

November–December 2003

EXOSAPARIN SODIUM DSD Mgh #29290

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	L# #	Dowex 1X8	Molar ratio of sulfate to carboxylate	1.5 cm x 2.5 cm, 200 – 400 mesh, Fluka catalog number 44339.
29(6)	L# #	Dowex 50W2	Molar ratio of sulfate to carboxylate	1.5 cm x 7.5 cm, 100 – 200 mesh, Fluka catalog number 44462.
29(6)	L# #	Dowex 1X8	Mol wt distrib, Ave mol wt	1.5 cm x 2.5 cm, 200 – 400 mesh, Fluka catalog number 44339.

ENOXAPARIN SODIUM INJECTION DSD Mgh #29295

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	L# #	IonPac AS11	Free	Free Sulfate content. Analytical column. 4 mm x 25 cm, manufacturer Dionex.
29(6)	L# #	IonPac AS11	Free	Free Sulfate content. Guard column. 4 mm x 5 cm, manufacturer Dionex.

GLIMPEPIRIDE DSD Mgh #35020

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	G43	Optima 624	Water	0.32 mm x 30 m, 1.8 :m film thickness, manufacturer Macherey-Nagel
29(6)	L20	LiChrosorb Diol	Limit of	Limit of cis isomer. 3 mm x 15 cm, 3 :m, manufacturer Merck KGaA.
29(6)	L1	Superspher 100 RP-18	Assay and Related Compounds	4 mm x 25 cm, 4 :m, manufacturer Merck KGaA.

METFORMIN HYDROCHLORIDE DSD Mgh #49795

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	L9	Partisil 10 SCX	Related compounds	4.6 mm x 25 cm, 10 :m, manufacturer Whatman, Inc.

METFORMIN HYDROCHLORIDE TABLETS DSD Mgh #49800

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	L9	Partisil 10 SCX	Related compounds	4.6 mm x 25 cm, 10 :m, manufacturer Whatman, Inc.

METOLAZONE TABLETS DSD Mgh #53470

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	L1	Symmetry C-18	Assay	3.9 mm x 15 cm, 5 :m, manufacturer Waters.

S-(ADENOSYL)-L-METHIONINE DISULFATE P-TOLUEN SULFONATE BULK SPRY DRIED POWDER DSD Mgh #704

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	L46	Ion Pac AS14A	Content of	Content of sulfate. 4 mm x 5 cm, :m, manufacturer Dionex.
29(6)	L1	YMC 18 ODS-A	Isomeric ratio	4.6 mm x 25 cm, 5 :m, manufacturer YMC Co., Ltd.
29(6)	L9	Supelcosil SCX	Assay, Related compounds, and Content of	Content of p-toluene sulfonic acid. 4.6 mm x 25 cm, 5 :m, manufacturer Supelco.

SUCCINYLCHOLINE CHLORIDE DSD Mgh #78520

PF	LGS#	Reagent Brand	Type of Test	Comments
29(6)	L1	XTerra MS C18	Limit of	Limit of choline. 4.6 mm x 25 cm, 5 :m, manufacturer Waters.
29(6)	L1	Alltima C-18	Chromatographic purity	4.6 mm x 25 cm, 5 :m, manufacturer Alltech.
29(6)	L1	Xterra MS C18	Chromatographic purity	Test 2. 4.6 mm x 25 cm, 5 :m, manufacturer Waters.
29(6)	L1	Alltima C-18	Chromatographic purity	Test 1. 4.6 mm x 25 cm, 5 :m, manufacturer Alltech.